

Brain Changes Associated With Pernicious Anemia

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of Philosophy, 1917

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BRAIN CHANGES ASSOCIATED WITH PERNICIOUS ANEMIA *

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The frequency with which symptoms referable to the central nervous system occur in anemic patients, particularly if the anemia be of the pernicious, or essential type, has long been recognized and made the object of extensive investigation.

While our knowledge of this baffling disease has made wonderful strides since Addison first described it in 1855, we have become more and more embarrassed by the seeming increase of our ignorance, and we need be little surprised when we see the chaotic state our problem was in some twenty years later. At this time, Schuele,¹ in an excellent study of three mental cases, in which there co-existed a severe anemia, expressed his opinion in this connection by saying: "It is apparent, granted that muscular degeneration can be of central origin, that anemias of neurogenic origin also exist;" and came to the general conclusion that atrophy of the cerebral cortex was, in his cases, the primary cause of the pernicious anemia. Other authors believed the anemia to be the result of some change in the spinal cord.

While the object of this study is the investigation of brain changes in essential pernicious anemia, it seems advisable to review some of the more important contributions to the literature on the changes found in the spinal cord in this disease.

Although Lichtenstern, in 1884, described two cases of pernicious anemia, complicated by spinal cord symptoms under the title, "Progressive Pernicious Anemia in Tabetics," in which he considered the pernicious anemia to be dependent on the tabes, it was not until 1886 that Lichtheim recognized the real significance of this syndrome, and to him is due the credit of establishing the true relationship of pernicious anemia to subacute combined degeneration of the spinal cord, and of stimulating extensive research in this field, out of which crystallized a great many facts fundamental in neuropathology.

While we now have a fairly clear idea of the pathologic processes involved, there still remain a great many problems which require

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1. Bibliography will be found at the end of the article.

further elucidation. This applies especially to the understanding of the exact mechanism by which these changes are brought about. Although there are still some writers who consider the anemia to be the chief factor in causing the degenerations of the spinal cord (Goebel), most writers have come to the conclusion that it is really a toxin, or several toxins which must be responsible for these alterations (Minnich, Nonne, Petren, Von Voss, Russell, Batten and Collier, Johnson, Reuling, Bonhoeffer, etc.).

That toxins alone are able to produce such changes, we know from the alterations which occur in the cord, which in many cases cannot be distinguished from those associated with pernicious anemia, when various poisons are introduced into the human organism; the same changes also appear as a result of certain poisons and in connection with certain morbid states; that is, lead, arsenic, ergot, pellagra, lathyrism, chronic alcoholism, diabetes, leukemia, severe secondary anemias, diphtheria, Addison's disease, tuberculosis, syphilis, typhoid, carcinoma, senility, chronic jaundice, malaria, leprosy, influenza, scarlet fever, tetanus, pregnancy, shock and tea (Gordon).

It was also pointed out that the nervous symptoms may precede the appearance of the anemia, sometimes by many months, which made the view that anemia alone might be the cause untenable (Minnich, Nonne, Bastianelli, Van Wart).

The fact that patients, having pernicious anemia, often have an elevation of temperature, was also taken to indicate that a toxin was at work (Lloyd). Von Voss, however, furnished the best evidence when he induced an anemia in laboratory animals by injecting pyrocin, glycerin, pyrogallol, and toluyldiamin, with the result that only one animal showed cord changes, and these were different from those occurring in pernicious anemia; no changes, analogous to pernicious anemia in the human, were found in these animals. Thus, anemia, per se, cannot be the cause of these lesions; the real cause, probably, being a toxin.

That the toxin, and not the anemia alone, is responsible for the cord changes, has thus become the generally accepted theory. As to its source, nature and mode of action, however, we are still completely at sea. If we were to accept Naegeli's view, that pernicious anemia is always a toxogenic anemia, coming from a variety of sources, notably such as the *Bothriocephalus*, pregnancy, syphilis, and malaria, and that a pernicious anemia may in reality, therefore, at times be a secondary anemia and amenable to treatment, the problem would become greatly simplified. His definition, however, is not accepted by all writers, and many, perhaps most of them, insist that a true pernicious anemia must be essential, or idiopathic, and some add, fatal, and that therefore, any

demonstrable etiologic factor would at once place it into the class of secondary anemias. This leaves us in a difficult position. Nonne evaded this difficulty by substituting the term "lethal anemias."

It may be in order here to remark that this looseness in the terminology must be kept in mind in reviewing the literature, and in interpreting the necropsy reports. Thus, for example, we again and again find syphilis present in the cases reported under the caption, "pernicious anemia"; the findings in such cases are obviously rather hazardous to interpret.

For this paper, therefore, I have used only such cases of anemia as would be classed under the term "primary idiopathic." With this slight digression, we can again turn our attention to a brief consideration of the theoretical toxin, or toxins, at work.

Minnich was the first to suggest that this toxin might be of gastrointestinal origin; more recently attention has been directed to the tonsils and teeth.

Blankenhorn, in a clinical study of the blood serum of pernicious anemia patients, made the observation that those patients, in whom the serum yielded the strongest Pettenkoffer reaction, showed, clinically, the greater involvement of the central nervous system. He, therefore, concluded that it was the presence of large amounts of bile salts in the blood that was responsible for these neurologic manifestations.

Our understanding of the mode of action of these toxins is little better. According to a good many authors it is but one toxin that is responsible for both the blood vascular changes, so frequently observed, and the neuronal degeneration (Johnson); others regard it as more selective in its properties, and consider this specificity, plus a difference in resistance, inherent in various structures of the central nervous system, as an explanation of the localization of the destructive process (Russell, Batten and Collier); still others insist that there must be at least two separate and distinct toxins at work, one having an affinity for the red blood cells, the other, an affinity for the fibers of the spinal cord (Reuling).

Von Voss, in discussing this phase of the subject, does not come to any such definite conclusions, but leaves the question *sub judice*; the changes may accordingly be due, (1) to one toxin causing both the anemia and the cord changes; (2) the toxin may be indirectly produced by the anemia, and then bring about the changes in the spinal cord; and (3) the anemia itself may act as a toxin, which through malnutrition causes the alterations in the cord.

The second hypothesis, in a slightly altered form, is also advanced by Bonhoeffer, who, in discussing the psychoses occasionally observed in pernicious anemia patients, does not consider these specific reactions

as due to a toxin, but supposes other changes in the brain cells themselves or in their metabolism to be interposed—a view gaining increasingly wider acceptance in analogous conditions, as, for example, between alcohol and delirium tremens, as opposed to alcohol and drunkenness.

That the lesions found in the central nervous system are the result of toxin action can hardly be questioned; nor can it be doubted that anemia in itself can and does render the nervous elements more susceptible to the actions of these toxins. Any further statements are purely hypothetical and unwarranted on the basis of our present knowledge.

A most animated discussion has been that which centered around the pathologic mechanism, instrumental in producing the so-called Lichtheim foci and the subsequent condition of combined sclerosis. According to the first theory advanced, it was the blood vessels which through hyalinization, thrombosis or rupture, were considered responsible for these lesions.

Minnich, in a series of five cases of pernicious anemia, free from neurologic symptoms clinically, and which subsequently came to necropsy, found no lesions whatever in the nervous system, other than multiple hemorrhages, which he studied in great detail. These he considered fundamental in the production of the Lichtheim foci, and believed them analogous to the multiple hemorrhages occurring in the retina, pleura, pericardium, intestinal serosa, and meninges. As to the alterations taking place in the vessel walls themselves, he assumed the process to be initial in the perivascular lymph spaces and supporting tissue, with resulting lymph stasis, perivascular sclerosis, intimal thickening, vascular sclerosis, and consequent tissue destruction. Nonne's views were essentially the same.

While probably the majority of writers, among them Burr, Bullock, Johnson and Marburg, mention vascular changes, such as proliferation and swelling of the intimal cells, hyaline degeneration, and often complete thrombosis, their conclusions are not the same.

According to Marburg, the localization of the pathologic process in the cord, corresponds to that area which is best supplied by blood vessels, and hence has transported to it the largest amount of toxin. Curiously enough, Brauwer and Blaukwip reverse this statement, saying that not the areas best supplied with blood, but those most poorly supplied, are the ones which suffer most extensively. Schmaus, here, as in multiple sclerosis, is a supporter of the lymph-stasis theory.

While the "vascular theory" was for a time widely accepted, it did not long go unchallenged. It was pointed out that not only did the blood vessels in the diseased areas too often look normal, but also

blood vessels in healthy areas too often were much diseased (Bastionelli, Russell, Batten, and Collier, Jacob, Moxter, Von Voss, Putnam and Taylor). It was likewise shown that in a great many cases there was no evidence, whatever, of hemorrhage (Russell, Batten, and Collier).

Relative to the lymph stasis theory, Lenel suggests that the swelling seen in the adventitial tissue may be only a stage in the "Abbauvorgang," and thus a result, rather than a cause, of the nerve lesions.

An entirely different explanation is advanced by Rothmann, who found hemorrhages, atrophy, and destruction of the anterior horn cells in the gray matter. These, he argues, as does Teichmueller, are the changes which initiate the cycle of disintegration, while the alterations seen in the white matter are due simply to a resulting secondary degeneration. He insists further, that although these lesions are not always demonstrable microscopically, the injury is there nevertheless, and the mechanism the same.

Goebel, on the other hand, though he also demonstrated changes in the gray matter, refutes this idea by saying that the changes in the gray matter are often missing, that the intensity and the localization of these changes do not correspond with those found in the white columns, and that in longitudinal sections, the commissural fibers are found to be intact. Additional evidence was supplied by Bastionelli, who noted that the white fibers were diseased only in the peripheral portions of the cord and that the gray matter, for this reason, could not be the primary seat of the degeneration.

On account of the evidences of inflammation sometimes observed, and the occasional febrile course, it is thought by some (Boedeke and Juliusberger) that the process taking place here is really a true myelitis of the disseminated type. This, Nonne thinks, is also true of sepsis and senility. The fact, however, that inflammatory reaction, such as cell infiltration, is too often lacking, and that the gray matter is only exceptionally involved (Billings) argues against this view.

Edinger, in support of his "Ersatztheorie" performed an experiment which has a direct bearing on the point under consideration. In the spinal cords of a number of rats, in which he produced an anemia, and which he then set to work by the ingenious device of suspending them by their tails, he found extensive degenerative changes, while in the cords of control rats, which were not anemic, no such changes could be detected.

Finally, Dana has emphasized two other factors, which may be at work in this disease and which may be instrumental, first, in determining the characteristic localization, and, second, in deciding which patients are to get a combined sclerosis, and which are to remain

altogether free from it. It is in reality the peripheral ends of the axones of the pyramidal cells and of the posterior ganglion cells that bear the brunt of the destructive process; this, he says, may be due to the distance of this portion of the nerve fiber from its trophic center. Relative to the second point, he suggests that this may be explained by individual predisposition; that those persons hereditarily endowed with "weak cords" will be the ones to suffer from a complicating cord degeneration, while those who were not so predisposed, will escape.

A not infrequent finding in the spinal cords of pernicious anemia patients is the presence of cavity formation (Bäumler, Camac and Milne, Bullock, Friedlander, and Henneberg). Boedeker and Juliusberger described peculiar stafflike structures as occurring, associated with a few of the anterior horn cells; these were at times scattered throughout the entire cell, at times in only a portion of it, then again partly within the cell and partly in the pericellular space, and sometimes entirely within the latter. These structures, stained green with iodine, red-brown with basic fuchsin, were present in the Marchi sections, and remained unstained with methylene blue, eosin, and hematoxylin.

While the foregoing is a rather fragmentary and disconnected review of this aspect of pernicious anemia pathology, it is not the object of this paper to enter on a discussion of the many theories advanced, save only in so far as may be necessary to explain the pathologic changes noted in the cortex.

The literature bearing on the clinical manifestations of cortical origin is not so voluminous as is that concerning the spinal cord; however, in recent years, attention has been directed this way, and numerous cases, in which psychotic manifestations were noted, have been placed on record. Already Addison, in 1855, when he first described the disease, spoke of the occasional wandering of the mind, and, indeed, a terminal delirium, usually of a mild type, is one of the commonest of the mental phenomena noted. There appears to be no law according to which these disturbances develop, and the psychic alterations may run the entire gamut of mental symptomatology.

In cases which develop some of the better defined types of psychoses, such as manic depressive insanity, it is probable that an individual predisposition was present, the pernicious anemia being really more or less independent of the mental disorder; when this has not been the case, however, the majority of writers have come to the conclusion that the individual may be altogether free from any neurotic tendency, the psychosis being then placed in the category of the exhaustion (Bonhoeffer, Meyer) or infection-intoxication psychoses (Siemerling).

Putnam and Taylor consider a neurotic tendency fairly common, and noted in their patients, as a rule, an exaggeration of native traits. Church describes the mental condition as one of a continuation of the dream state, which these patients cannot shake off on being roused and which usually subsides spontaneously on further stimulation. Picket, from a study of seven cases, gives the composite mental picture of these patients as a shallow confusion with impairment of ideas of time and place, increasing on awakening from sleep; illusions, particularly of identity, are common. Hallucinations and persecutory delusions may arise. "The pernicious anemia is mainly an abeyance of the mind." Very often the psychosis may simulate a general paresis (Marcus, Camp); Korsakow's syndrome has also been noted following a delirious condition (Bonhoeffer).

Just as cord symptoms may appear long before there is any evidence of the underlying pernicious anemia, so mental symptoms may appear in persons who may be somewhat anemic, but in whom the diagnosis of pernicious anemia would not be warranted. This was well shown in a case reported by Marcus, and also emphasized by Langdon, who in a series of cases, some of the patients having definite pernicious anemia, others having more or less severe anemia, designated the condition as "pre-pernicious anemia." Likewise, these symptoms are strikingly transitory, and usually improve, *pari passu*, with an improvement in the physical state (Grawitz).

Kraepelin, although he discusses the relation of anemia to psychoses at some length, does not mention pernicious anemia in particular, and concludes by saying that it is not clear whether the anemia is a causative factor or an accidental accompanying condition.

The contributions of Barrett are particularly illuminating. Among 650 necropsies on insane persons in Michigan, he reports that there were fifteen cases of pernicious anemia, and suggests that this disease may play a larger rôle in psychiatry than is now supposed. In his first study of nine cases, two resembling dementia praecox, one manic-depressive insanity, and six asthenic with paranoid feature, he concluded that, as a whole, these patients had in common, irritability and suspiciousness, which formed the groundwork for delusions of persecution, the content of which was generally influenced by the somato-neurologic symptoms. In several cases hallucination and confabulation occurred, suggesting a Korsakow's psychosis. There was no marked deterioration, and comprehension and orientation were usually clear, except for a rare episode. In two instances there was slight expansion. In a number of cases there were remissions in the mental condition which ran parallel to those on the physical side. In all but one there was a hereditary predisposition, which he regards as of considerable

importance. He classifies these cases among the paranoid conditions which are symptomatic of a toxic-organic process affecting the central nervous system, analogous to those found in tabes, alcoholism, and certain drugs intoxications.

Only a few of the cases reported present symptoms referable to other parts of the central nervous system, outside the cord. Among these optic atrophy stands first and has been several times noted (Russell, Bastionelli, Putnam and Taylor, Bramwell). Collier, however, declares it to be a decidedly uncommon occurrence, having been found but once in fifty-eight cases, and in this one instance, being probably of syphilitic origin.

Various attacks of cortical origin have been described, such as a sudden feeling of cold and death in an extremity (Eichorst), light hemiparesis of the face (Immermann), passing hemiplegic attacks (Mueller, Nonne), which may be accompanied by convulsive seizures (Mueller and Bierner), diplopia (Russell, Batten, and Collier), sudden severe headaches (Hawthorn), and total blindness from extensive softening of the occipital lobes (Wicher).

As to the pathologic lesions found in the brain itself, comparatively little has been published. Birulja, in 1894, found numerous small blood extravasations, accumulations of lymphoid cells, pigment masses, and diminished tincture with carmin. Ransohoff noted inflammatory foci in the brain and cord. Mott described marked changes in the corticopyramidal cells, and on examinations with the Marchi method, showed degeneration in the whole pyramidal system, from the cortex downward. Spiller, however, takes exception to this diagnosis and looks on it as a case of amyotrophic lateral sclerosis, associated with anemia. This author found changes as high as the middle of the pons, which he considered retrograde. Preobrajensky has described two types of foci occurring in the medulla, cord, and cerebellum—1, miliary sclerotic foci accompanying the blood vessels, and 2, miliary foci from disintegration of the nerve substance.

Schroeder regularly finds miliary foci occurring in the brain in lethal anemias, not found in other diseases. These differ somewhat from the Lichtheim foci and are usually about 80 to 100 microns in diameter, globular or slightly oblong, always isolated, and generally widely separated from each other; they are in close relationship to the blood vessels, each one having a capillary in its center, and display no selective localization. They are most readily found in Nissl-stained sections, in which the center appears clear, containing sometimes a few blood cells, and the periphery blue, being made up of more or less degenerated glia cells. These "Ringwallherdchen" have no relation to the plaques found in the spinal cord.

Barrett has reported findings in eleven cases, which are exceedingly interesting. The Nissl bodies he found often markedly disintegrated, a few cells showing the characteristic axonal degeneration. The neuroglia cells were, as a rule, moderately increased and had a tendency to group arrangement; in some of them mitotic figures were noted. Rod cells and cells of odd shapes were present in the cortex in considerable numbers. Degenerative changes in the blood vessels and pigment deposit were common. The striking finding, however, was that of typical Lichtheim plaques in four of the eleven brains examined, ten of which showed distinct pathologic changes. These changes, he concludes, were such as occur in conditions of chronic intoxication and resemble those found in chronic alcoholism. He also found in one of the brains (Case 2, M. T.) the foci described by Schroeder.

Pfeiffer, in a very careful histologic study of the cortex, found a good many cellular changes, the most frequent of which was swelling of the ganglion cells, invariably associated with hyperpigmentation. These changes are similar to those found in psychoses of toxemic origin.

REPORT OF CASES

Seven brains, in all, were available for study. These had been fixed in formaldehyd solution and were now cut in the frontal plane so as to obtain sections about 8 mm. in thickness through the entire brain, from each of the following levels: (1) section just anterior to the genu of the corpus callosum; (2) section 0.5 cm. posterior to the optic chiasma; (3) section through the center of the cut surface of the crura cerebri, the cerebellum and pons having been removed; (4) section cutting through the posterior end of the splenium corporis callosi; (5) section through the middle of the pons and that portion of the cerebellum overlying it; (6) section through the medulla and the cerebellum at the middle of the olive. These blocks were then mordanted, imbedded in parlodion-celloidin being practically off the market—cut under alcohol, by means of the large Edinger microtome, into sections 50 to 100 microns in thickness, and stained by the Weigert and the Pal-Weigert methods, the Van Giesen counterstain being added to some of them.

Since the Weigert sections of four of these brains showed marked evidences of disease, frontal sections cutting through the entire brain at levels corresponding to the Weigert sections were also prepared and stained with osmic acid according to the method of Marchi; supplementing these, Marchi sections were also prepared from certain other areas of these brains. The Marchi sections from the remaining three brains, while not cutting through the entire brain, were sufficiently large and numerous to permit a careful and satisfactory study. Silver sections were prepared by the Bielschowsky method, the pyridin modification for the preparation of serial sections as well as the method described for frozen sections, being employed. For general histology and cell study, representative areas of the cortex were stained by means of hematoxylin and eosin, thionin, toluidin blue, and neutral red. The *Lichtgruenfuchsin* stain, devised by Alzheimer, was employed for the demonstration of fuchsinophilic granula. Glia fibers and cells were studied by means of Weigert's glia fiber stain and the new gold stain recently developed by Raymón y Cajal. The larger blood vessels at the base were stained with hematoxylin and eosin and with Weigert's elastic stain in various combinations.

CASE 1.—(Necropsy 14-113). *History.*—The history shows the following: G. M., 51 years of age, married, traveling salesman and a blender and taster of wine for twenty-five years, presented himself for examination Dec. 4, 1912. His father died of heart trouble at the age of 42, and his mother of stomach trouble at the age of 62. One brother and two sisters were living and well. His general health was good up to the age of 40, with the exception of a nervous, rundown condition for two or three months when he was 15 years old, during which time he was not confined to bed and from which he recovered completely. He also had measles, whooping cough, and was rather ill with chickenpox. There was no diphtheria, scarlet fever, pneumonia or typhoid. Syphilis and gonorrhea were denied. Up to fifteen years previous to the examination he used considerable wine and whisky, but since that time had been more moderate. He had always been a rather hard worker. He married at 22, had one child, and his wife had one miscarriage, due to accident. He was married again at 33, there being no pregnancies during the second marriage. Eighteen years previously he received a slight injury to his back, which pro-

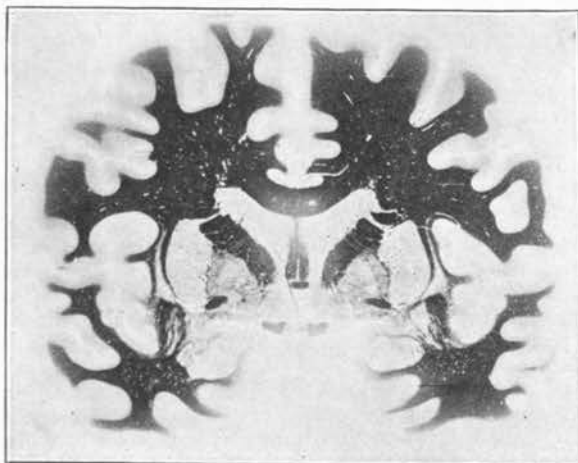


Fig. 1 (Case 4).—Weigert's myelin sheath stain. Cross section of brain, showing gross appearance of degenerative foci, analogous to the so-called Lichtheim plaques occurring in the spinal cord in cases of pernicious anemia.

duced no symptoms at the time. About this time he also was considerably jaundiced and complained of pain and tenderness over the gallbladder region. He suffered a good deal from indigestion, but this bothered him little during the last four or five years. He also has been constipated for years. His present illness began in January or February, 1914, during which time his legs became easily cold and would ache, mostly in the shins and feet. This ache was sharp rather than dull, and was present especially when cold. He gradually began to get stiff in the legs; this at first caused no trouble in walking, but later on the toes began to catch. About three months previously he experienced some tightness about the waist, which was now largely gone. Two months previously he began to stagger in walking, which increased until about a month and a half previously, since when he had been unable to walk alone. For the previous two weeks there was also some drawing in the legs, together with a sensation of burning in the legs and buttocks. At this time he was said to have been rather pale. For one week or more he had some difficulty in urination, which began with sharp pains in the scrotum; the water was slow to start and dribbled at the last. He also had considerable difficulty in getting his bowels to move.

Of late his appetite had not been very good. He always felt much worse in cold than in warm weather. For the previous two days there had been some edema of the left ankle. His color was fair, but growing somewhat pasty.

The systolic blood pressure taken on the day of examination was found to be 116 mm. Hg.

Neurologic Examination.—The neurologic examination showed the following: *Cranial Nerves:* The sense of smell was found to be normal when tested with perfume. Vision was practically normal and the field of vision was good to a rough test. There was no central scotoma. Fundus examination was not very satisfactory but the eye ground appeared to be normal in the right eye. There was no diplopia, no nystagmus, and movements of the external ocular muscles were normal. The pupils were circular, the right being a little smaller than the left. Reaction to light was rather sluggish and reaction to accommodation normal. Functions of the seventh and eighth nerves were normal, as were also the tuning fork tests. Sensation over the distribution of the fifth

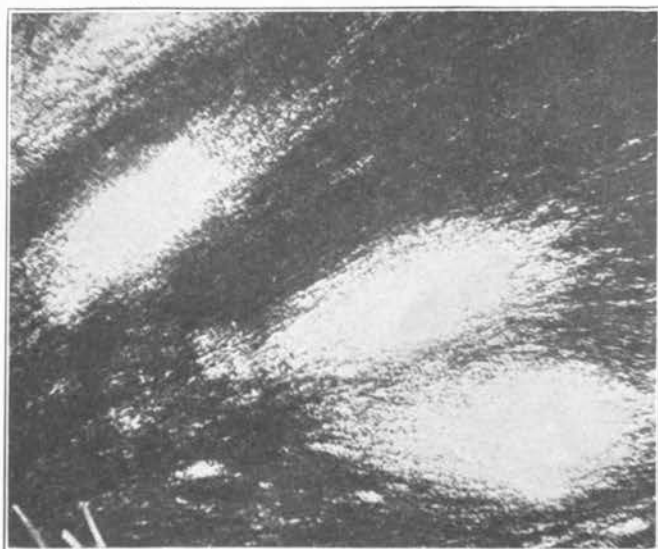


Fig. 2 (Case 4).—Weigert's myelin sheath stain. Lichtheim type of focus present in the corpus callosum. Magnified about 20 diameters.

was normal, save that the conjunctival reflexes were sluggish. The ninth, tenth, eleventh, and twelfth cranial nerves were normal. The speech was a little peculiar, however, it was probably always so. *Muscles:* There was some jerking of the legs, each jerk being accompanied by a sharp pain. The patient stated that this jerking was always aggravated when he became cold or very hot. The dynamometric test of the hands registered about 38 on the right and 30 on the left. The abdominal recti were normal. In the legs there was moderate weakness of the anterior thigh group on the right and great weakness on the left. The anterior tibial group was normal on the right but impaired on the left. Power in the calf muscles was poor on both sides. There was no special tremor of the extended fingers. *Reflexes:* The deep reflexes of the arm were a little below normal. The abdominal reflexes were all missing except twice, when a slight response in the right lower abdomen was obtained. The scrotal reflex was absent. Both knee kicks were very active. There was a double ankle clonus of rather short duration, somewhat better sustained on the left than on the right. Scratching for the Babinski reflex was decidedly painful on the

right, less so on the left; the left plantar was constantly extensor, the right was at first flexor and then extensor. *Sensation:* The patient said that he could feel the clothing on his feet and cutaneous sensation was practically normal everywhere except for some slight impairment on the plantar surface of the toes of both feet and over the left shin. Subjectively, there was some numbness and prickling in the hands which was worse when he became cold. The patient said that at times he did not know where his legs were, though he had an appreciation of the movement in his toes when wiggling them. Joint sensation in the toes was completely absent when tested objectively and impaired to a considerable degree in the ankle. Vibration sensation in the legs was normal. All stroking of the abdomen and chest with a dull instrument was painful. Coordination in the hands was fairly satisfactory, though there was a little awkwardness in handling things. In the legs there was distinct ataxia. Stereognosis was normal.

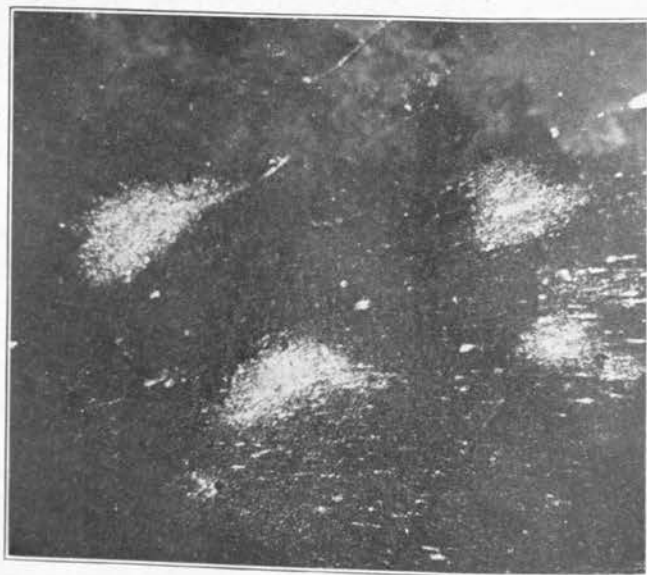


Fig. 3 (Case 2).—Weigert's myelin sheath stain, Van Gieson counterstain. Plaques of degeneration found in the centrum semiovale, crus level. The one seen in the upper left hand corner is of the "palm-tree" type, in which the degeneration occurs at the point of bifurcation of a capillary.

Course.—Jan. 1, 1913. The patient complained of some numbness and stiffness in the hands and arms. Practically all the swelling of the left foot and leg had disappeared. The patient said that he could pass water into a cold urinal, which he could not do before.

Jan. 19, 1913. The pupils were a little small and reaction to light and distance was normal. Both legs jerked considerably. The deep reflexes of the arms were rather sluggish. The upper and lower abdominal reflexes were faint and the right was soon exhausted. The cremasteric reflexes were absent. Both Achilles tendon reflexes were active. There was a slight patellar clonus on both sides, as well as an easily exhausted ankle clonus, which was somewhat better on the left than on the right. There was a distinct Babinski phenomenon on the left, while on the right the plantar reflex was at times extensor, though usually flexor. There was possibly a slight disturbance of tactile sensation from the seventh rib downward, though there was no disturbance of pain sensibility.

save possibly in the feet, where he often called the head of a pin the point. The patient was sensitive to tapping and stroking of all parts of the body. Joint sense in the hands seemed to be normal. The patient said that he still lost his legs at times, though he could usually tell when one leg was on top of the other, and which it was. Joint sense in the toes was almost completely lost. Vibration sensibility was present over the malleoli and over the shins.

Feb. 5, 1913. The patient raised his legs from the bed fairly well; though the left was somewhat weaker than the right. The deep reflexes in the arms were not increased. Both patellar reflexes were very active; there was a patellar clonus present on the left and a very faint patellar clonus on the right. There was a slight double ankle clonus of short duration. The Babinski phenomenon was positive on the left and doubtful on the right. Bowel and bladder control was good.

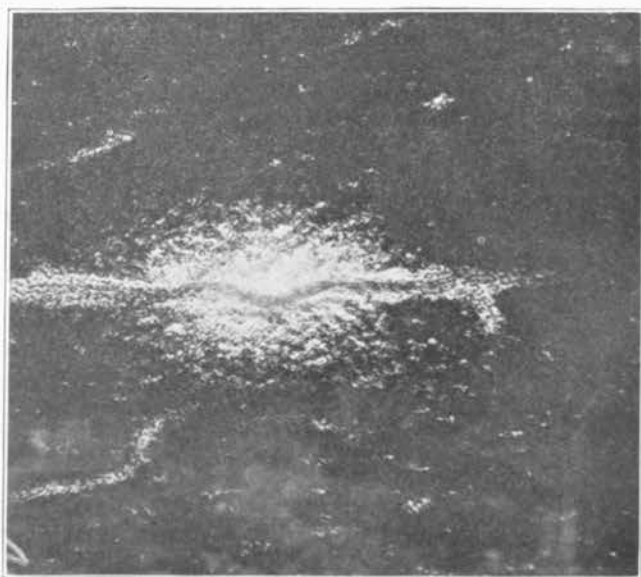


Fig. 4 (Case 4).—Weigert's myelin sheath stain. Another illustration of the relation which these plaques sometimes bear to blood vessels. This particular one was present in the fibers of the optic radiations.

June 7, 1913. The patient was getting out of doors and walked with the assistance of a cane and the occasional support from a building. His legs were very stiff. He had never been quite wholly free from the prickling sensation and thought that it was a little worse of late. The grip of the right hand registered 45 and of the left 35. The right plantar response was flexor and the left doubtful. There was no clonus. On the plantar surface of the right index finger he felt pin pricks a little less distinctly than on the left side. The blood pressure was 154 mm.

June 22, 1914. Last winter the patient grew considerably worse and did not improve much during the summer. He began failing mentally, was extremely irritable and unreasonable, and several times struck at his wife. He had had distinct spastic phenomena and a good deal of sensory impairment. When seen two days ago there was distinct hypotonia and no clonus could be obtained. He ultimately became very stupid and died without any special further change.

Necropsy.—Death occurred June 22, 1914, a necropsy being performed while the body was still warm. The necropsy protocol was as follows:

The body is that of a well developed, well nourished man, 168 cm. in length. There is slight rigor mortis in the upper extremities. Lividity is present in the dependent portions. The pupils measure 5 mm. in diameter and are equal. There is no edema. A few small ulcers are present on the posterior surface of the sacrum. The peritoneal cavity contains no excess fluid. The subcutaneous tissue anteriorly is 2.5 cm. in thickness. The appendix is 12 cm. in length and is bound down by a few old adhesions. The diaphragm extends to the fourth intercostal space on the left and to the fourth rib on the right. The pleural cavities show small fibrous adhesions at the base of the right lung with no excess of fluid in either cavity. The pericardial cavity contains no excess fluid. The heart is normal in size, the epicardium and endocardium are clear and smooth, and the valves thin and soft. The myocardium is of a pale reddish color and fairly firm. The root of the aorta shows no gross lesions. The

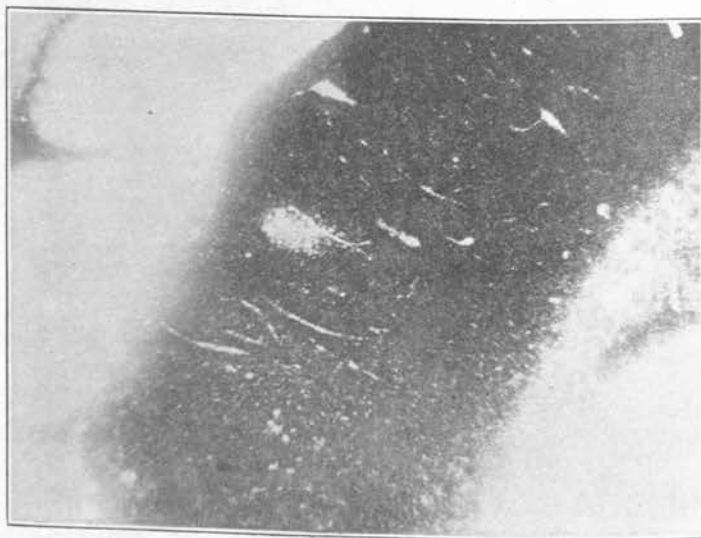


Fig. 5 (Case 2).—Weigert's myelin sheath stain. Lichtheim focus, associated with a small blood vessel, present in the brachium conjunctivum.

lungs crepitate throughout and the posterior portions are somewhat heavier than the anterior. The cut surfaces show a small amount of bloody, frothy exudate. In one area of the right lung, a small amount of pus can be expressed from the bronchioles. No nodules are palpable. The spleen shows a slightly wrinkled capsule. The cut surface is of a reddish color and fairly firm. The pulp scrapes with some resistance. No special markings are visible. The liver is somewhat smaller than normal, the capsule is smooth and clear, and the cut surface shows no special features. The pancreas and gastrointestinal tract appear normal. The adrenal shows no gross lesions. The kidneys are of normal size. The capsules strip with a little resistance. The cortices are about normal in thickness and the demarcation between the cortex and the medulla is fairly sharp. The bladder and genital organs were not removed. On removing the dura mater, the subarachnoid space is found enormously distended with a thin clear fluid. The arachnoid is thin and translucent. The arteries of the brain are soft. No pathologic condition is present in the brain substance from external examination. The subarachnoid space of the

cord is distended with a thin clear fluid. Sections of the spinal cord in the cervical, thoracic, and lumbar regions show areas of degeneration in the white substance which are rather diffuse, except in the cervical region where the column of Goll is sharply circumscribed and degenerated. The bone marrow from the central part of the shaft of the right femur is of a yellowish white color. In the upper third of the femur, near the posterior portion, the marrow is found to be of a deep red color.

Microscopic Examination.—The heart shows several small areas of fibrosis. The lungs and adrenals appear normal. The liver shows a marked atrophy of the hepatic cords with a small amount of pigment. There are also evidences of a slight chronic passive congestion. The kidney shows a few small patches of fibrosis near the capsule, but is otherwise normal. The spleen shows some atrophy with a hyaline degeneration of the arterioles. In the spinal cord the majority of fibers of the white columns are degenerated; this is especially marked in the posterior and lateral columns; those fibers which are in con-

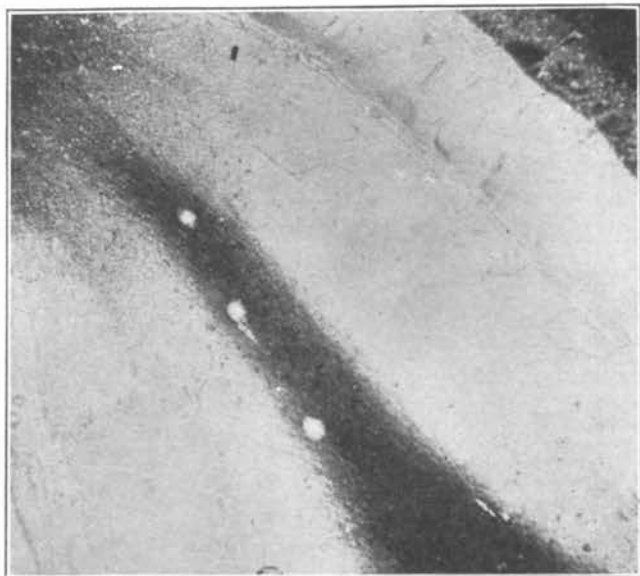


Fig. 6 (Case 2).—Weigert's myelin sheath stain. Gyrus fusiformis, showing the small circular foci found in the medullary substance just underlying the marginal gray layer, corresponding probably to miliary foci described by Preobrajensky.

tact with the gray substance are not degenerated. The bacteriologic examination of the heart's blood shows no growth. A smear made from the pus expressed from one of the bronchioles shows bacteria of various kinds. The anatomic diagnosis was as follows: 1. Combined sclerosis of the spinal cord; 2. edema of the brain; 3. pernicious anemia (?).

Examination of Brain.—The brain is of normal size and rather pale. The membranes are somewhat opaque along the blood vessels and show some edema. The convolutions are normal in appearance. The blood vessels at the base are moderately thickened and slightly tortuous. A few slight atheromatous patches are also noted.

Weigert Sections: Sections through the frontal lobes: On the right side of the brain, a little above the midline, and well within the substance of the

centrum semiovale, are a dozen or so irregular areas, about 0.5 mm. in width and 1 to 2 mm. in length, in which the white fibers do not stain. These areas are associated with capillaries which they sometimes surround concentrically, though more often lying somewhat or altogether to one side; the edges are irregular and ill defined and there is a distinct tendency for the degenerated areas to spread in the direction of the fibers. *Sections through the level of the chiasma:* Grossly there is seen a small triangular area of degeneration in the upper portion of the lenticular nucleus, in the angle between the internal and external capsules, also a smaller area in the upper and outer portion of the caudate nucleus. Areas of degeneration, similar to those described above, are seen in great numbers in both semiovale areas, though somewhat more on the right than on the left, in the corpus callosum, and in the optic tract near

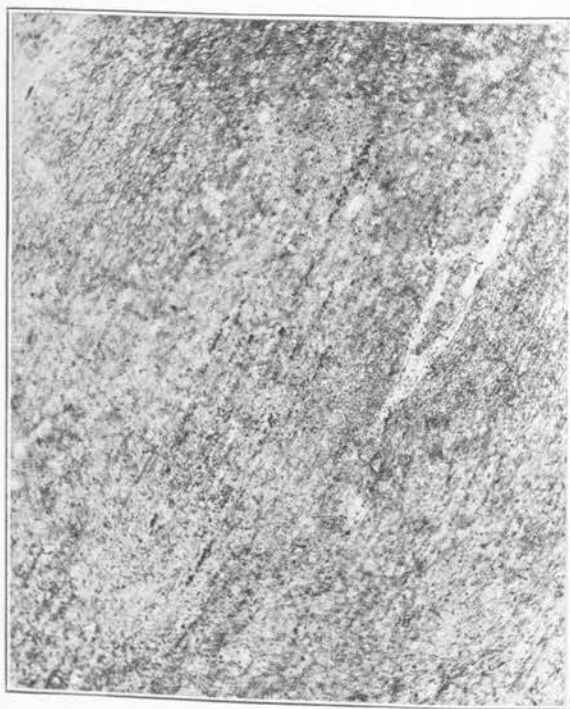


Fig. 7 (Case 4).—Marchi stain. $\times 50$. An area of degeneration, constituting possibly an early stage in the production of a Lichtheim plaque. Second temporal gyrus.

the chiasma. *Sections through the level of the crus:* With the unaided eye one can see a sharply defined, wedge-shaped area of degeneration, the base of the wedge being directed upward, which involves the outer quarter of the putamen. The upper and outer portion of the caudate nucleus shows a similar degeneration about the size of a pea. Areas of perivascular degeneration appear scattered throughout the white matter. They are more numerous on the right side, where there are some twenty in number, than on the left, and are also seen in number, in the corresponding area on the left, in the corpus callosum and in the fornix. Under the microscope these changes are found to be more ballooning of the myelin sheaths is seen, particularly at the periphery of some of these areas. *Sections through the occipital lobes:* The same areas of degeneration

eration appear but are less numerous than in the preceding section. They are particularly numerous in the corpus callosum and in the fourchette, although they occur in smaller numbers in all other portions of the white matter. In the marginal gray layer of the gyri, is seen, surrounding some of the blood vessels, a distinct halo. *Sections through the cerebellum:* Under the dentate nucleus is found an area of perivascular degeneration similar to those described above. *Sections through the pons:* In the left brachium conjunctivum is a typical Lichtheim focus with marked ballooning of the fibers. A similar but somewhat smaller focus is seen in the left brachium pontis. Other structures in this section appear normal.

Marchi Sections: Sections through frontal lobes: The sections show a rather diffuse degeneration of moderate intensity with some accumulation of pigment in the perivascular spaces. There are also seen a number of relatively pale areas, with poorly defined margins, surrounding some of the blood vessels. The corpus callosum shows no more degeneration than is found in



Fig. 8 (Case 1).—Marchi stain. $\times 50$. Area of extensive degeneration in centrum semiovale, level of the crus.

other portions of the section. The pyramidal cells are all rather more deeply pigmented than is normally seen. *Sections through level of chiasma:* There is a diffuse, rather marked degeneration throughout the white matter of the section, which is particularly prominent in the fibers passing from the surface toward the internal capsule. Small, circular, pale areas, which are rather sharply defined, appear in moderate numbers in both the marginal gray and the submarginal white matter. The pyramidal cells of the cortex appear normal. *Sections through level of crus:* Here are seen very numerous foci, formed by deposits of blackened granules, most of them having a definite relation to the blood vessels; these are particularly numerous in the centrum semiovale, where the degeneration is very intense. As the crus is approached, the degeneration is seen to be older, on the whole, though recently degenerated fibers are scattered throughout. Although the degeneration is most marked around the blood vessels, the intervening areas also show a considerable disintegration of the

nerve fibers. That portion of the cortex occupied by fibers of the optic radiations, also shows a marked deposit of small and somewhat dusty granules. All stages of degeneration can be followed in various parts of the section: The primary ballooning and browning of the fibers, the formation of Elzholz corpuscles, chains of coarse black beads, disintegration of these into finer granules, and their transport in "Abbauszellen," to the perivascular spaces. The pyramidal cells which overlie these areas contain no more than the normal amount of pigment. The basal nuclei are normal in appearance, save for the accumulation of a small amount of perivascular pigment. *Sections through occipital lobes:* Grossly one can see pale areas, presumably perivascular, which appear somewhat as was noted in the Weigert sections. The degeneration of this portion of the cortex is well marked and most intense in the fibers of the optic radiations and of the corpus callosum. As in the preceding sections, all stages of degeneration can be noted. Perivascular areas of degeneration are seen here and there, together with varying amounts of fatty accumulations. The pyramidal cells here are rather markedly pigmented, particularly in the lower

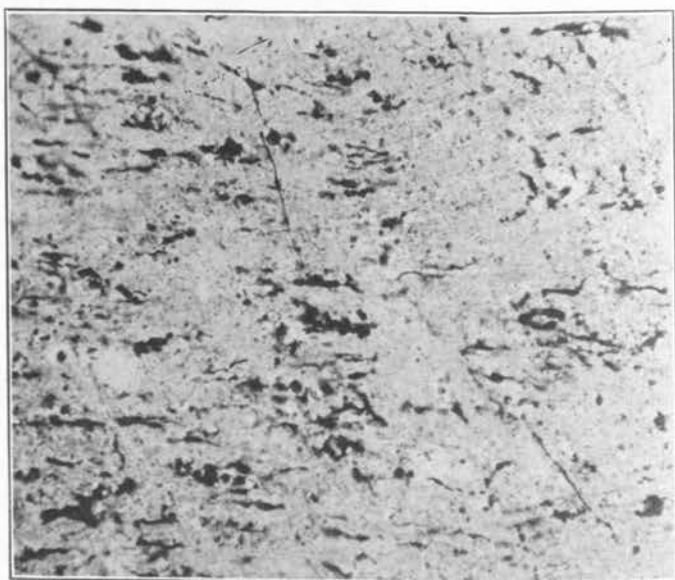


Fig. 9 (Case 1).—Marchi stain. $\times 100$. Portion of Figure 7, under higher magnification.

portion of the occipital lobes, some of the cells, and this is notably true of those in the third pyramidal layer, being in many instances completely replaced by pigment. There appears to be no definite relationship, however, between the degree of hyperpigmentation of these cells and the degeneration of the fibers underlying. *Sections through olives and the overlying cerebellum:* There is a rather diffuse degeneration noted throughout the white matter of the section. In the cerebellum this is particularly marked in the peduncle of the flocculus and in those fibers which descend from the dentate nucleus, where the evidences of degeneration are marked. In the cross section of the medulla, degeneration of the pyramidal tracts is rather marked, these being thereby sharply demarcated from the other parts of the section; there is also evidence of degeneration, which is older than that seen in the pyramidal tract, in those areas occupied by the spinocerebellar tracts. A rather slight degree of stippling is seen throughout the remainder of the section occupied by the white matter. *Sections through*

the brain stem at the level of the corpora quadrigemina inferior: There is a rather extensive degeneration in the formatio reticularis and a somewhat milder grade of degeneration in the lateral and medial fillets, where there is a good deal of pigment accumulated in the perivascular spaces. The pyramidal tracts show a like degree of disintegration, with typical beadlike formation of Marchi granules, where some of these fibers have been cut in a slightly longitudinal direction. The small amount of stippling in the brachium pontis is probably pseudo-Marchi in character. *Sections through the upper portion of the pons and medulla, at the level of the fifth nerve:* Here a moderate degeneration is seen in the median fillet and in the pyramidal tract. There is also some blackening of the fibers evident in the intramedullary portion of the fifth nerve as well as in those fibers which pass over the brachium conjunctivum, which may belong either to the lateral fillet or to Gowers' tract. The remainder of the section is perfectly clear.

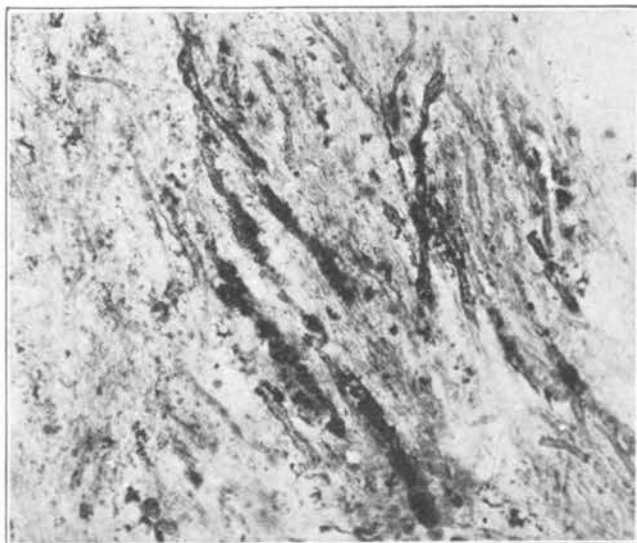


Fig. 10 (Case 4).—Marchi stain, $\times 100$. Showing degeneration present in the corpus callosum. Cross section of brain just posterior to optic chiasma.

Bielchowsky Sections: In the serial Bielchowsky sections are seen many blood vessels which are surrounded by areas lighter in color than the surrounding tissue, from which they are not sharply demarcated, in which the fibers appear to be disintegrated; axis cylinders, on passing through such an area, tend to become pale, somewhat granular and ultimately to disappear. The neurofibrilli within the cells do not stain well, in general, though in those instances in which they can be seen, they look entirely normal.

The neuroglia tissue, on the whole, as seen in the Weigert glia-fiber and in the Ramón y Cajal glia cell sections, appears to be normal, though there is possibly a diffuse increase in the glia cells and in the glia processes, some of which appear to be very massive and wavy, particularly in those sections prepared from the frontal lobe.

In the sections stained with hematoxylin and eosin are found certain areas in the white matter which are of a pale, grayish-blue color, varying in size from 0.01 to 0.1 mm. in diameter. These areas look as though they might have been produced by some distention of the interfibrillar substance, there being no

particular change in the surrounding tissue. As a rule the margin is fairly sharp. In a good many instances this same cribriform appearance can be seen surrounding the perivascular spaces, which probably correspond to the areas of the same size seen in the preceding sections. In a number of instances the nuclei of glia cells within these areas can be seen in various stages of degeneration, as shown in Figure 13. These changes are especially noted in the temporal gyri and about the calcarine fissures. In the right putamen, near the ventricular wall, is seen a fairly recent hemorrhage about 1 mm. in diameter.

Thionin, toluidin blue and neutral red sections: On the whole these sections present a fairly normal appearance. The cyto architecture is undisturbed and the cells stain fairly well, although the Nissl bodies are not as distinct as one normally sees. A few of the cells show a rather indistinct outline, which is often much distorted, and the dendrites are usually poorly defined. Vacuoles of varying sizes can be observed, and the nuclei are often eccentric and in several instances partially extruded. These changes occur to some extent

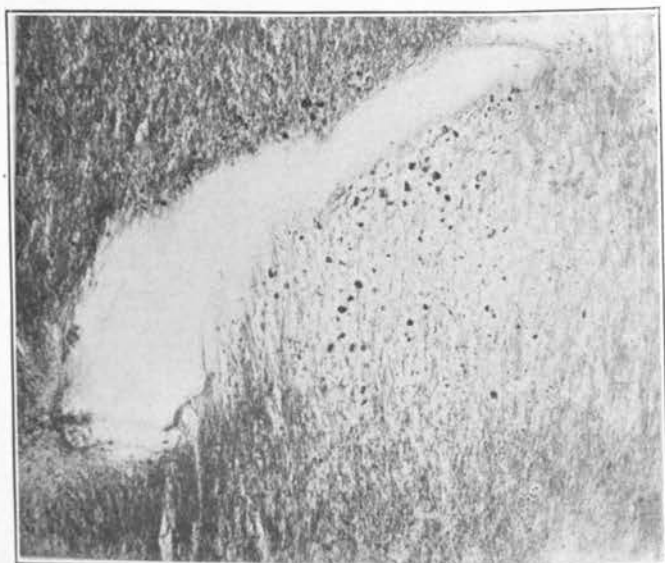


Fig. 11 (Case 3).—Marchi stain. $\times 100$. Area of degeneration in proximity to blood vessel. Compare with Figure 14.

in all of the layers but are found most marked in the deep and superficial large pyramidal cells. Typical axonal reaction was found in two or three instances in sections from the right Rolandic area. All of these changes, with the exception of the axonal reaction, were found particularly marked in the frontal, Rolandic, and temporal lobes. In sections from the calcarine area one also finds a slight degree of perivascular, small, round cell infiltration. The cerebellum and basal nuclei showed no changes of interest.

In the fuchsin-lichtgruen sections, 3 microns in thickness, prepared according to Alzheimer's instructions, most of the cells appear practically normal, though a good many contain, scattered throughout the cell, small, brilliant-red, fuchsinophilic granules, which vary in number from two or three to twenty or more granules to a cell. One cell was found completely filled with such granules. This stain also shows very beautifully the granules which are stained black by the osmic acid of Flemming's solution, some of them being very small, others very large, evidently formed by the coalition of the smaller granules.

The blood vessels at the base show a moderate hypertrophy, principally of the media, though the intima also shows a slight thickening. This hypertrophy is concentric and uniform throughout the periphery of the vessel. The elastic tissue is normal in amount.

CASE 2.—(Necropsy 759). *History*.—Mr. A. R. S., 42 years of age, engaged in railroad construction, doing very hard work and being very much exposed, presented himself for examination May 19, 1908. He was married, had four children, three of which were living and well and one of which died of spina bifida. His father died at 77 years of age of an unknown cause and the mother at 65 of "cold." Two brothers died from excessive use of liquor, and one brother, a twin with the patient, died when he was 1 week old. There are three brothers living and well. During the first six months of his life the

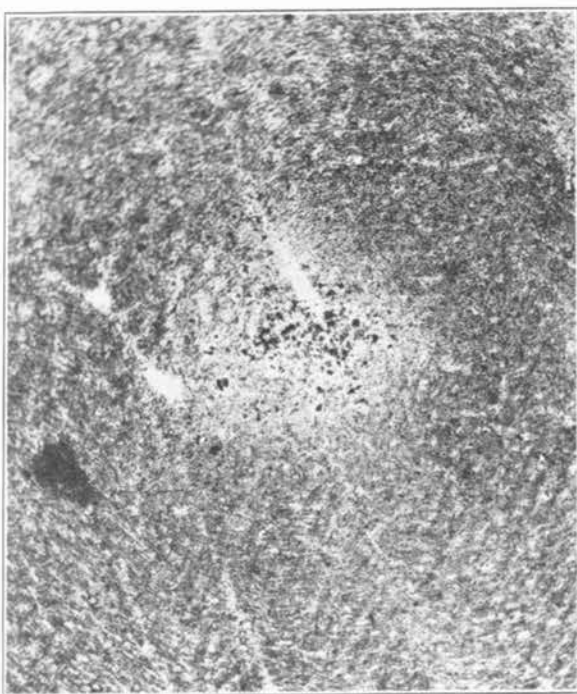


Fig. 12 (Case 2).—Marchi stain. $\times 50$. Showing an area of perivascular degeneration and accumulation of "Abbauszellen."

patient was weakly, but after that grew well and strong. Had measles, scarlet fever, and diphtheria in childhood but was never seriously ill. He had a Neisserian infection about fifteen years and again eight years prior to examination, from which he recovered. Denied having ever had syphilis. For ten years the patient was a very heavy drinker, but said he had taken nothing during the previous six years. In June, 1905, he was struck on the head by a bar which left no contusion or lump, though he regularly after that noted an occasional sharp pain in the top of his head. Some four months later the scalp broke and there was a discharge of a little pus; two weeks later the diseased area was cut out and in a short time his scalp was wholly well. He had no other injuries of consequence. About the same time the patient noticed that he wanted more clothing for sleep than formerly. At that time he had completed a hard three

days' tramp in the rain, going almost wholly without food. He said that he had never been well since. He also noticed that he became more easily irritated than before. During all this time he noticed no anemia. Since then his health had varied somewhat and at times he would feel entirely well, and then, for a few days would have a vague sense of being unwell. In November, 1906, he noticed a beginning numbness in his fingers and in his toes, and in two weeks this sensation spread through the arms and legs to the body, where it had been present more or less ever since. He also noticed trouble in walking, which bothered him a good deal for three months. Always slept well until this time, but since then he had been bothered somewhat with insomnia. About this time he began to be very pale and suffered some from shortness of breath. He began taking cold water baths and massage and gained in weight from 185 to 210 pounds, but caught cold, after which he felt very sore for two or three days and lost all the weight he had gained. In March, 1908, he visited

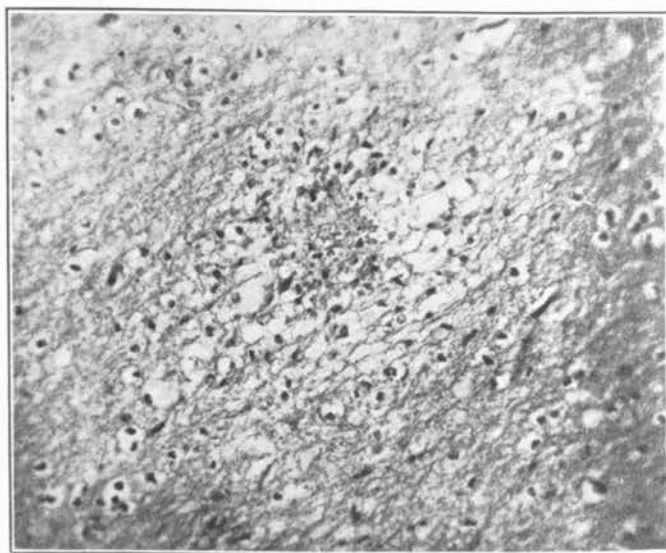


Fig. 13 (Case 3).—Hematoxylin and eosin. $\times 200$. One of the sieve-like areas occurring in the medullary substance. This one was located near the sensory-motor area and contained a more or less necrotic center.

the Mayo Clinic, where his case was diagnosed as pernicious anemia. For nearly a month he improved very much but again caught cold and lost all previous gain. Since then he had also had much pain in the base of his head and more recently between the shoulders and in the hands and arms. There was also some numb feeling in the legs. There were no shooting pains in the legs or cramps in the abdomen. The bowel and bladder control was normal at the time of examination.

Examination.—On examination the patient appeared to be extremely anemic and the skin had a lemon yellow hue. His weight was 180 pounds. There was a double inguinal hernia. The patient walked with the greatest difficulty and it was not possible for him to stand with his feet close together. The pupillary reactions were normal. The tongue was distinctly tremulous, moderately coated and projected straight. When first seen there was a marked increase in the patellar and Achilles tendon reflexes and objective tests revealed a little sensory disturbance. There was an ankle clonus on both sides and a double Bab-

inski phenomenon. Subsequently, though his anemia was growing steadily worse, his reflexes gradually approached normal, finally became diminished, and ultimately disappeared. There was some diminution of touch and pain sensibility in the hands and in the feet, and a very marked loss of joint sensibility in both the hands and the feet. Toward the end he developed marked mental symptoms which began with some degree of mental sluggishness, and just preceding death developed into a distinct delirium. His blood, examined on March 30, 1908, showed hemoglobin 47 per cent.; red count 1,700,000; color index 1.3+; 3,000 leukocytes, a few myelocytes, and some anisocytosis. April 6 the hemoglobin was 47 per cent.; April 11, 35 per cent.; May 4, 57 per cent., and May 11, 53 per cent.

Necropsy.—The patient died Sept. 8, 1908, necropsy being performed twenty-one and a half hours after death. The notes showed the following: The patient was a well developed person, with fair general nutrition. The body had

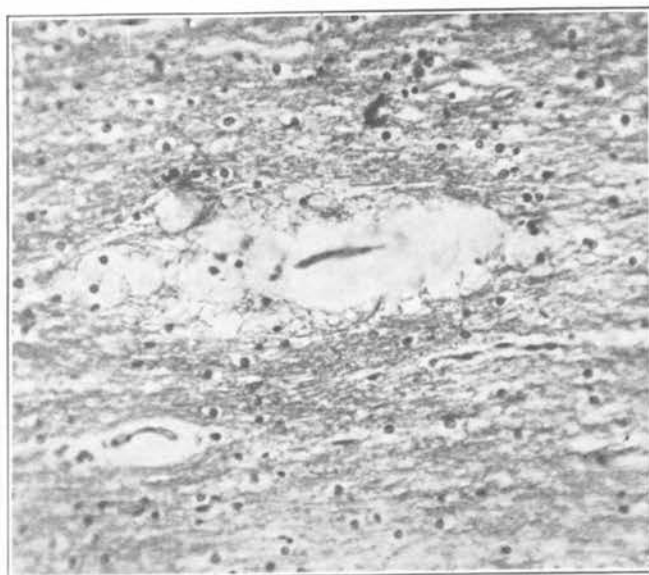


Fig. 14 (Case 5).—Hematoxylin and eosin. $\times 200$. Section cutting through the left calcarine fissure, showing one of the numerous sieve-like areas, in this instance surrounding a blood vessel.

been injected with formaldehyd solution and contained scarcely any blood, all cavities being filled with this artificial fluid. There was well marked lividity. The heart was moderately enlarged and revealed a chronic valvular endocarditis of the aortic, bicuspid, and tricuspid valves. Both left and right sides of the heart contained large chicken-fat clots. There was a moderate thickening of the intima of the aorta. The spleen weighed 282 gm. and showed, microscopically, a hyaline thickening of the blood vessels. The kidneys appeared to be normal at necropsy, though microscopically they showed an occasional sclerosed glomerulus. The lungs showed some thickening of the pleura and the alveoli contained a good deal of serum in the dependent portions of the lung and an occasional polymorphonuclear leukocyte. The adrenal was the seat of a new growth, possibly a hypernephroma. The bone marrow was lemon yellow in color. The liver and the gastro-intestinal tract were normal. The pancreas showed a slight fatty change. The pituitary gland was somewhat congested and showed a slight increase in connective tissue.

Brain.—The dura was normal in appearance, the sinuses were practically empty, and there was no evidence of pachymeningitis. The brain was pale and gray-white in color. There was a marked edema of the pia-arachnoid, but no opacity. The contour of the brain and of the convolutions was normal in appearance. The ventricles were of normal size and the ventricular walls were smooth and glistening. Fixation was good. The blood vessels at the base showed no evidence of arteriosclerosis, the walls being very thin and tender. The spinal cord showed a marked combined sclerosis of the type seen in pernicious anemia.

Weigert Sections: Frontal sections: There is a certain amount of perivascular degeneration present. In the medullary portion of the gyri, just under the gray layer, are found several small, circular, fairly sharply demarcated areas 0.1 to 0.2 mm. in diameter. There are about nine of these to the low power field. A few are also noted in the gray layer. *Sections posterior to*

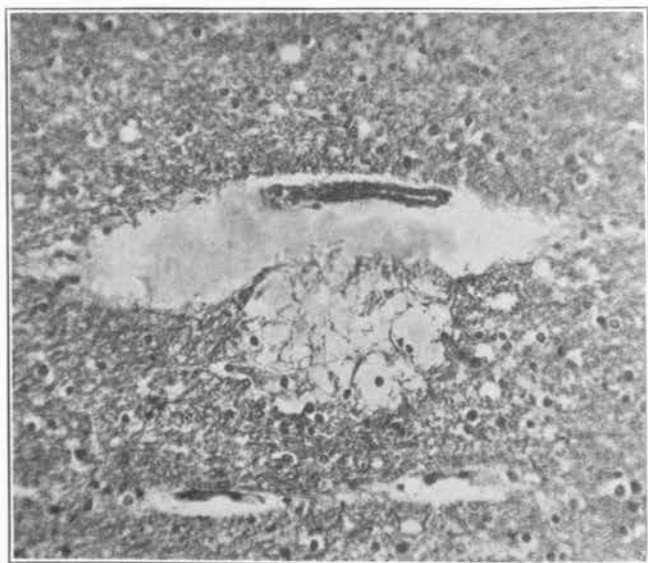


Fig. 15 (Case 5).—Hematoxylin and eosin. $\times 200$. Same area as above figure. The substance filling the gland-like structure at the side of the vessel is seen to be filled with a hyalin-like material, basophilic in reaction, and resembling in all respects the material present in the perivascular space, from which it appears to have been crowded into the tissue. Compare with Figure 10.

optic chiasma: There is a very definite area of perivascular degeneration 0.2 by 0.4 mm. in size in the centrum semiovale, also one in the corpus callosum. The blood vessels appear to be normal. *Sections through the middle of the crus:* Some fifteen to twenty typical Lichtheim plaques are noted in each centrum semiovale, also a number in the corpus callosum. These are about 2 by 3 mm. in size, and are usually associated with the blood vessels. In one instance a capillary is seen to be perfectly normal in appearance to its point of bifurcation, where a large degenerated area is found, the entire structure resembling a palm tree, as shown in Figure 3. In the gray matter of the gyri one finds a few of the pale globular areas described in the preceding case. *Sections through the occipital lobes:* There is considerable perivascular degeneration present in many places throughout the white matter. The sharply outlined circular areas, described as occurring in the medullary portions of the gyri, are found

here also. *Sections through the pons:* In the right brachium conjunctivum a perivascular area of degeneration can be seen. *Sections through the olives and the dentate nucleus:* Perfectly typical Lichtheim foci of small size, with disappearance and ballooning of the myelin sheaths, are seen in both corpora restiformes and in the pyramidal tracts. In all other respects, these sections are normal in appearance.

Marchi Sections: Frontal sections: The small, circular, white areas seen in the Weigert sections just below the gray layer can be seen here as relatively pale areas. There is a very slight and diffuse stippling throughout the section, which is more marked in the fibers of the corpus callosum than elsewhere; the major part of this, however, is probably pseudo-Marchi in character. *Sections through the optic chiasma:* These sections are practically normal in appearance except for a slight deposit of granules in the perivascular spaces in the gray matter. *Sections 0.5 cm. posterior to the chiasma:* There is a definite though moderate degeneration in the fibers of the corpus callosum; the optic

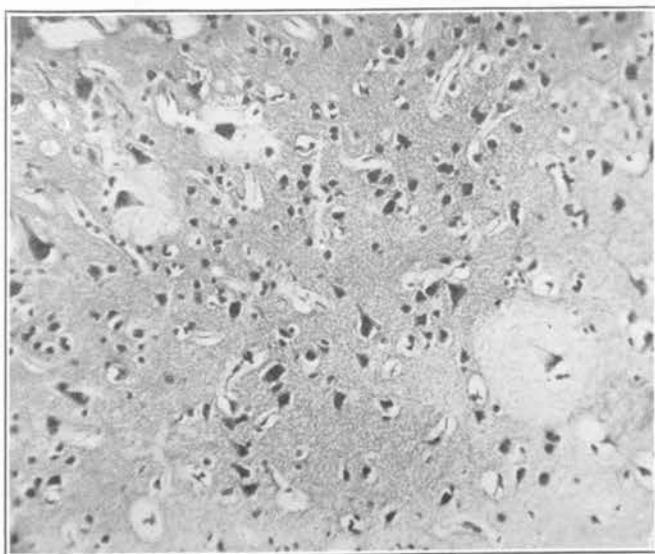


Fig. 16 (Case 3).—Hematoxylin and eosin. $\times 200$. Left pre-Rolandic gyrus. Three areas of pericellular destruction are noted, the lower right hand one being reproduced at a higher magnification in the following figure.

tract is also moderately degenerated and shows the perivascular space of one of its blood vessels filled with an accumulation of pigment. *Sections through crus:* A slight stippling is noted throughout the section, which is uniform and which may not exceed that seen in a normal case. There is, however, a very distinct, though rather slight degeneration of the fibers in the optic radiations. The blood vessels throughout the section show a slight deposit of pigment in the perivascular spaces. Surrounding some of the blood vessels, both in the gray and in the medullary portions, is a pale halo. This is probably the counterpart of the light perivascular areas seen in the Weigert sections. *Sections through occipital lobes:* The degeneration in this portion of the brain is more definite than that seen further forward. A number of blackened areas can be seen occurring about some of the capillaries of the medullary substance which are composed of degenerated nerve fibers and "Abbauszellen." *Sections through the pons and the overlying cerebellum, cutting through the dentate nucleus:* There is a striking degeneration in both corpora restiformes, which is more pro-

nounced on one side than on the other, in which there appears a marked ballooning of the fibers, together with an extensive deposit of Marchi granules. There is also a definite, though less intense, degeneration in the fibers of the pyramidal tract, together with a slight, diffuse degeneration of the remaining portion of the medullary substance. In the vicinity of the dentate nucleus, particularly among the descending fibers one also sees some degenerating fibers. *Sections through the pons, at the level of the decussation of the fourth nerve:* There is a somewhat diffuse degeneration of moderate intensity in the fibers of the pyramidal tracts, in the median and lateral lemnisci, in the substantia reticularis, and in the decussating fiber of the fourth nerve. The blood vessels in these areas show a moderate amount of perivascular deposit. A smaller and somewhat thinner section taken through the temporal lobe shows probably some increase in the pigment of the cells, some of them, particularly those in the third temporal convolution, being almost a solid black. The majority of cells, however, do not contain any excess pigment. The degeneration of the short com-

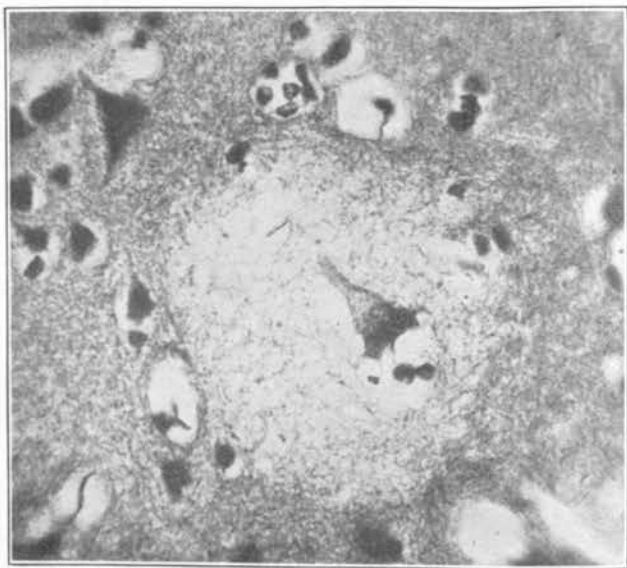


Fig. 17.— $\times 500$. Showing in greater detail the pericellular area of tissue change. The pyramidal cell itself is practically normal in appearance. Two satellite cells are seen.

missural fibers is apparently just as marked as is that of the longer fibers, and in the case of the third temporal convolution, there appears to be no more degeneration of the fibers than is seen elsewhere in the section. A longitudinal section of the internal capsule shows a slight, rather diffuse degeneration of these fibers; the blood vessels show only very slight perivascular deposits.

Bielchowsky Sections: In the Bielchowsky slides one sees rather poorly defined elongated areas, which are paler than the surrounding tissue and which are usually, though not invariably, associated with blood vessels, as becomes evident from a study of the serial sections. These areas are formed by a rather pale staining, somewhat granular, flocculent material; the approaching axis cylinders are seen to become pale, wavy, granular, and finally disintegrated. A number of apparently normal fibers can usually be seen passing through these areas. Sections taken from the thalamus are normal, except for the presence of a perivascular area similar to those just described.

The glia fibers and glia cells of this brain are perfectly normal in appearance. In sections stained with hematoxylin and eosin, one sees a number of pale areas, of uncertain definition, in which the fibrillar structure is seen grouped in somewhat coarse, wavy bundles. These areas are particularly numerous in the Rolandic and occipital areas of the brain, and probably correspond to the lighter areas seen in preceding sections. Some of these show a rather diffuse increase in glia cell nuclei. Sections stained with thionin and toluidin blue show the pyramidal cells to be practically normal in appearance, save for a slight tigrolysis and occasional eccentricity of the nuclei. In the right Rolandic area one sees a moderate amount of satellitosis. Two instances of axonal degeneration were found in sections selected from the left precentral gyrus. In the right first temporal gyrus is seen a blood vessel filled with polymorphonuclear cells. The cerebellum appears to be perfectly normal. In some of the overstained sections there are seen in the marginal gray layer, pale, more or less circular areas; these

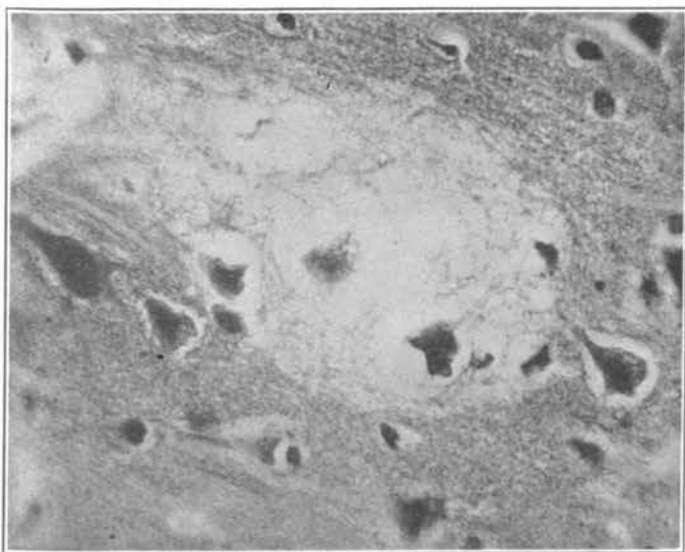


Fig. 18 (Case 3).—Hematoxylin and eosin. $\times 500$. Pre-Rolandic gyrus, superficial large pyramidal cell layer. Two pyramids are shown, in different degrees of degeneration, the lower one being only moderately involved, while the upper one shows a more marked destruction. A neuronophage is seen in the lower cell also.

not infrequently have in their center a nerve cell which shows sometimes slight, at other times very marked, evidences of degeneration. Only one such area containing a cell was found in the *lichtgruenfuchsin* preparations, the cell being perfectly normal in appearance. Four or five similar areas were found, though no cell could be seen in their center. No fuchsinophilic granules could be found, all the cells being apparently normal.

CASE 3.—(Necropsy 767). *History*.—G. W. S., aged 40, married and a housewife, presented herself for examination May 20, 1908. The father died at the age of 78 and the mother of some intestinal trouble, which may have been tuberculosis. There were three sisters living, one of whom had diabetes. There is some neurotic tendency in the family, and the patient herself had been nervous for the previous three or four years, and the previous winter began exercising. She incidentally took cold and subsequently there developed a sen

sation of needles being pricked into her back and also a sensation in the foot as though the arch were falling. There later developed a feeling of weakness and numbness in the legs, which in the course of time reached her knees, thighs, and back. The patient gradually grew very much weaker and finally died, a diagnosis of pernicious anemia having been made. Unfortunately there was no full record of her examination at hand; it was known, however, that the patient showed a very marked increase in her patellar reflexes.

Necropsy.—A necropsy was performed Sept. 20, 1908, the record of which follows: The body is that of an adult, well developed, but considerably emaciated female. Rigor mortis is well marked and there is slight lividity. The sacrum is a site of a moderate sized bed sore. The abdominal, pleural and pericardial cavities contain no fluid. The lungs are normal in appearance except for a few small areas of anthracosis and a number of peribronchial lymph nodes. The heart is normal in size, rather flabby and shows no evidence of endo-

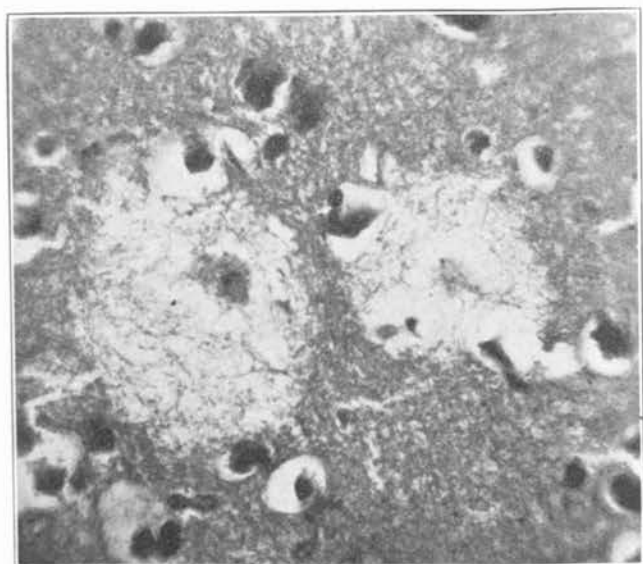


Fig. 19 (Case 3).—Hematoxylin and eosin. $\times 500$. Two pyramidal cells of the left superior temporal gyrus, surrounded by a zone of pallor, undergoing disintegration, only a trace of the pyramid to the right remaining.

carditis. The spleen is moderately increased in size and cuts with increased resistance. In the kidneys of both sides are a very few small infarcts; the pyramids are distinctly congested, and the capsules, though somewhat thickened, strip readily. Microscopically are seen a few areas of hemorrhage and an occasional sclerosed glomerulus; scattered throughout the section are many foci of lymphoid cells. The liver shows some cellular infiltration of the border connective tissue, but is otherwise normal in appearance. The spleen is practically normal save for some congestion and a hyalin thickening of the vessel walls. There are some adhesions between the right ovary and the intestine. The adrenals, pancreas and gastro-intestinal tracts present no pathologic changes. Cultures from the heart blood, spleen and liver showed a growth of *Staphylococcus pyogenes aureus* in all.

Brain.—The scalp and the skull are normal. The dura is free, practically normal in appearance, and the sinuses almost empty. The brain is of a very pale, grayish-white color. The vessels at the base are perhaps a trifle thickened

and stand open, but there is no atheroma present and they feel soft. The choroidal vessels are normal in appearance. The pia arachnoid shows considerable edema and is slightly opaque. The convolutions are perhaps a trifle shrunken and the sulci a little deep over the convexity. The ventricular walls are smooth and glistening. There is possibly some dilatation of both ventricles, the left being a little more dilated than the right. The spinal cord shows a very marked subacute combined sclerosis, such as is seen typically in cases of pernicious anemia.

Weigert Sections: Frontal area: Two or three small but characteristic areas of degeneration, such as are found in the spinal cord, are seen in this section, which are unassociated with blood vessels. Surrounding a blood vessel, which was cut longitudinally, is seen an area of disintegration of the myelin, which is present in only a limited portion of its course, the rest of the surrounding tissue being normal in appearance, as shown in Figure 4. In the medullary substance, under the cortical layer of gray matter, are seen a number of more



Fig. 20 (Case 1).—Ramon y Cajal's gold stain for glia cells. $\times 500$. Illustrating the massive and wavy glia cell processes noted in some of the brains.

or less circular areas of degeneration about 2 mm. in diameter, similar to those described in the preceding case. In certain locations they appear to push aside somewhat the radii passing into the gray matter. *Sections passing through the posterior portion of the optic chiasma:* The right temporal lobe, the island of Reil, and to a less extent the internal and external capsules, are rather pale and uniformly gray in color. In this area there is seen a marked increase in the number of small blood vessels, all of them being 1 mm. or less in diameter. The inferior temporal gyrus on this side is in part definitely softened, with cavity formation. The perivascular spaces are seen to be enlarged and filled with a granular debris. The temporal lobe on the left shows a somewhat similar change, save that the softening is less advanced, and the myelin more deeply stained. The blood vessels in this locality are present in somewhat increased numbers and are comparatively large, some of them up to 2.5 mm. in diameter. Many of these vessels are surrounded by diffuse areas of degeneration which are elongated in the course of the nerve fibers. The other findings are very

much as in the preceding section. *Sections through the middle of the crus:* The same area of diffuse, partial softening is noted in the right temporal lobe and presents the same characteristics noted above. This also holds true for the left side, though the blood vessels here are somewhat smaller. Ballooning of the fibers can be seen in many of these areas. The small circular areas, described as occurring in the medullary portion of the gyri, are seen here also. *Occipital area:* The diffuse area of degeneration on the left side is seen in this section to extend from the lateral wall of the ventricle toward the periphery, where there is a margin of apparently normal tissue. There is some dilatation of the blood vessels in all portions of this section. *Sections through the cerebellum:* In several of the laminae of the cerebellum are seen one or more pale, fairly well defined circular areas which resemble those described in previous sections. *Sections through the pons and the cerebellum:* Except for the finding noted in the preceding section the tissue was apparently normal.

Marchi Sections: Frontal area: Grossly there are seen in the superficial gray layer a number of light points which are usually circular, though sometimes elongated and branched, as though accompanying blood vessels. Microscopically there appears some diffuse stippling which, however, is probably pseudo-Marchi in character. No recent areas of degeneration can be detected. Slight perivascular accumulations are present here and there. The cells of the cortex contain about the normal amount of pigmentation. *Sections through the chiasma:* In the white matter are seen areas which are paler than the surrounding tissue, and which resemble in their general outline those seen in the Weigert sections. These are present in considerable numbers, particularly in the centrum semiovale. Microscopically, very marked degeneration is seen, which in places appears in the form of very small foci which probably represent the earlier stages of the Lichtheim plaques. As a rule these are associated with blood vessels, though this is not always evident. In these areas swollen fibers appear in great numbers and in all stages of transition from the blackened fibers to those completely disintegrated into fat droplets. "Abbauszellen," which contain these droplets as very fine, dustlike particles, can be seen surrounding some of the capillaries in great numbers. *Sections through the level of the crus:* There is a moderate amount of rather diffuse disintegration in the substance of white matter, particularly in the fibers passing through the internal capsule and in the corpus callosum. The pyramidal cells of the marginal gray are in places rather deeply pigmented; this is especially marked in the gyrus cinguli where in many instances the entire cell seems to be wholly filled with pigment globules varying greatly in size. As far as the lighter areas of the gray matter are concerned these are also found, in very few numbers, however, in the basal ganglia, the island of Reil being more or less free from them. *Occipital area:* A rather marked degeneration is present throughout the medullary substance. Blood vessels, which appear to be numerous and dilated, show a considerable amount of perivascular accumulation. *Sections through the pons at the level of the corpora quadrigemina inferior:* These sections are practically normal in appearance, save for a slight amount of perivascular deposit.

Bielchowsky Sections: In the Bielchowsky sections in the marginal gray layer are seen fairly numerous, pale, more or less circular areas with margins that are somewhat poorly defined. The centers of these areas are traversed by fibers which become paler as they pass into them from the surrounding tissue, often being lost in the relatively structureless center. The frequency with which pyramidal cells are seen to occupy the centers of these areas, forces the conclusion that they must in some manner be related to the so-called pericellular lymph space of Obersteiner. Unfortunately the intracellular fibrilli failed to stain clearly in these sections, though the cells, in other respects, appear to be about normal. Similar areas, though in lesser numbers, are also seen in the medullary substance, where they might be likened to localized patches of edema, giving the structure a more or less sievelike appearance.

The glia fibers and cells appear in this brain to be perfectly normal and show little, if any, evidence of reaction even in the vicinity of the softened areas in the left temporal lobes.

In section stained with hematoxylin and eosin, the pale foci described in the preceding sections of this case can be studied particularly well. They are most numerous in the gray layer overlying the gyri, appearing in numbers as high as six to ten to the low power field of the microscope, and found to be most numerous in the convolutions of the temporal lobe. They are seen, as a rule, to be more or less circular, then usually surrounding a pyramidal cell or somewhat elongated, in which case they generally follow the course of a vessel. The cells themselves which are found within these areas, not infrequently show degenerative changes. Somewhat larger patches, though similar in other respects, are found in the medullary substance of the gyri. Within the right temporal lobe is found an area of softening with a cavity about 1 cm. in diameter, surrounding which is a diffuse zone which shows evidence of mesodermal reaction. There are also seen in this portion of the cortex numerous hemorrhages of small size. The internal capsule and basal nuclei appear to be perfectly normal. In the thionin and toluidin blue sections the foci which have been described as occurring in the marginal gray layer can be studied to the best advantage. All stages of their formation, from their very incipency, in which there appears a very narrow haze surrounding some of the pyramidal cells, to their fullest development, in which they appear as a broad halo surrounding the cells more or less concentrically, can be traced. The cells themselves, in some instances, appear perfectly normal, in others there is seen a rather marked tigrolysis and eccentricity of the nucleus, and in still others is noted in addition, a varying degree of vacuolization. One of these cells showed a very marked degree of tigrolysis, loss of cell processes, marked vacuolization, partial extrusion of a swollen, rather deeply stained and ill defined nucleus with a pale nucleolus enlarged about three times its normal size, and eight satellite cells, four of them neuronophages. In another instance this area surrounded the base of one of the larger pyramidal cells which showed tigrolysis and a moderate degree of vacuolization. These changes are most marked in the second pyramidal layer. The size of the surrounding area and the degree of destruction of the cell seem to bear no definite relationship toward each other; however, those cells which show the highest degree of disintegration are usually surrounded by halos of considerable size. A good many of them are found in which only the residue of a destroyed pyramidal cell can be seen. This change is most marked in the temporal lobes, though the right and left frontal, the right and left Rolandic, and the right and left occipital gyri all show it to some degree. In a section of the left calcarine area is found, in the layer of stellate cells, a circular, rather deeply staining, more or less coarsely granular area about 50 microns in diameter, which is in turn surrounded in about four fifths of its circumference by a very narrow reef of similar material. The whole structure looks as though it might have been derived from disintegrated glia cell nuclei, and, although it does not correspond in all of its details to the foci described by Schroeder, it was the only lesion found in any of these brains which approached in appearance the plaques described by him. Aside from these changes, which are very obvious, the majority of cells show little in addition to a certain amount of tigrolysis, some eccentricity of the nuclei, which in certain instances are more deeply stained than normal, and a fairly marked degree of satellitosis. In a few instances there is complete disintegration of the cell. All of these changes occur with greatest frequency in the second and third pyramidal cell layers. The sievelike areas, described in preceding sections as occurring in the medullary portion, are found here also, but present no additional features. In no instance does there appear to be any increase in the glia cell nuclei. Near one of the capillaries in the left internal capsule there is found a clump of streptococci without evidences of surrounding tissue reaction.

Cells which present a moderate number of fuchsinophilic granules are fairly numerous, though none found within the pale areas of the gray matter are seen to contain them.

CASE 4.—(Necropsy 142587).² H. W. L. first visited the clinic Oct. 4, 1915. He was 48 years of age, married, and a farmer. His health in the past had been good, save for some chronic pain for twenty-five years in his knee which had a number of lumps on it. About two years previously an operation had been done on the knee, from which two calcareous masses, the size of a flattened plum, were removed. Soon after this he noticed that he was growing weak, that the color of his lips and nails was pale, and that his feet and hands became somewhat numb. His appetite was also poor and he became gradually weaker, lost in weight and was generally run down, but was not compelled to go to bed. July, 1914, he noticed that he would become dizzy on slight exertion and that his heart would palpitate easily. At about this time he was operated on for some stomach distress, which resulted in a negative exploration. After the operation he felt somewhat better and did some work in the fall of 1914. In December, however, he was compelled to go to bed where he remained for three months on account of weakness, after which he regained strength and was able to be up and about, off and on, until one month prior to his examination. Since then he had been bedridden and suffered from profound weakness. He also had some vague gastric distress but no hemorrhages; he had no appetite and, a month previously vomited every evening for a week. Fowler's solution and Bland's pills had been administered. There were no genito-urinary complaints.

Examination.—The physical findings showed a marked pyorrhea. There was extreme weakness, pallor, and much loss of weight which could not be accurately secured on account of his weakened condition. The systolic blood pressure was 80, the diastolic 20, and the pulse 100. In the calf of his right leg there was a muscle stone the size of a flattened plum. The blood examination on October 4 showed 18 per cent. hemoglobin, 1,030,000 red cells, color index 0.8+, and 4,600 leukocytes. A differential count of 300 cells was made, which showed 47.3 per cent. polymorphonuclears, 46.3 per cent. small lymphocytes, 4.3 per cent. large lymphocytes, 1.7 per cent. eosinophils, 0.3 per cent. basophils, 2 normoblasts, moderate anisocytosis, slight poikilocytosis, a moderate granular degeneration of the erythrocytes, and slight polychromatophilia. The hemoglobin during October showed on the seventh, 28 per cent., the eighth, 27 per cent., the eleventh, 45 per cent., the thirteenth, 38 per cent. October 6, one pint of blood was transfused. November 4, the blood count was as follows: 30 per cent. hemoglobin, 2,000,000 red cells, 0.7+ color index, 8,600 leukocytes, with a differential count of 39.7 per cent. polynuclear neutrophils, 53 per cent. small lymphocytes, 5.7 per cent. large lymphocytes, 1.3 per cent. eosinophils, 0.3 per cent. basophils, 36 normoblasts, moderate anisocytosis, slight poikilocytosis, and polychromatophilia. The diagnosis of pernicious anemia was made. October 15, a splenectomy was performed, at which time it was noted that gallstones were present, but these were not removed.

The patient returned June 20, 1916. On leaving, in October, the patient returned to his home and spent most of the time in bed, being quite weak. He was bothered a great deal with palpitation of the heart on little exertion. His legs were very unsteady and sensation in his feet was diminishing.

Neurologic Examination.—A neurologic examination, made July 5, showed the right pupil to be larger than the left. A watch was heard 4 inches from the ear on the left, and a normal distance of 30 inches on the right. Touch, pain and temperature were slightly impaired over the face, as compared to the

2. The clinical data and the pathologic material of the following case were obtained through the kindness of Drs. Walter D. Sheldon and Wayne W. Bissell of the Mayo Clinic, Rochester, Minn.

chest. The muscles were uniformly weak. Tactile sensation was very much diminished in the fingers and moderately diminished below the wrist, gradually increasing to normal above the mid forearm. It was almost completely absent in the feet, was moderately impaired above the ankles and increased gradually to normal, 6 inches above the knees. Pain sensibility was moderately impaired in the hands, increasing to normal as in touch. In the toes it was almost completely absent, increasing gradually to normal above the knees. Temperature sensation was moderately impaired in the hands, increasing to normal as in touch, and somewhat more impaired in the feet, increasing as above. Vibration sensation, tested with a tuning fork of 256 v., was absent over all bony prominences below the third lumbar spine. Joint sensibility was normal in the fingers and slightly impaired in the toes. Muscle pain sense was normal. The biceps, triceps and supinator reflexes were very active. The upper, middle and lower abdominal reflexes were normal on the right and moderately impaired on the left. The patellar tendon reflexes were normal, as was the left Achilles tendon reflex, the right being obtained only on reinforcement. There was a rather marked Romberg. The gait was slow and weak. Speech was slow, but otherwise normal. Coordination was normal in the finger-nose test and perhaps slightly impaired in the heel-knee-toe test. There was no tremor. A diagnosis of subacute combined sclerosis was made. The patient was transfused three times, first on June 25, when 500 c.c. of blood were transfused by the sodium citrate method; then, July 17, when the same amount was transfused, and again on August 9, when 600 c.c. were transfused. An examination of the duodenal contents showed the same to be dark yellow in color and gave the following values, estimated by the Schneider method: Bilirubin + + +, urobilinogen (3.4×200) 700, urobilin (5×200) 1,000, making a total of 1,700 units.

Aug. 22, 1916. A full neurologic examination at this time was impossible on account of the patient's weakened condition. When seen he had jerking movements of the right arm which came on every few minutes. Relatives said that this was also present in the left arm and both legs and even in the head and body. There was subjective numbness in the arms to the elbows, and in the body below the belt. The right pupil was larger than the left, and immobile to light, which may possibly be accounted for in part by the morphin which was required to allay the acute excitement from which he at times suffered. Pin pricks were felt in the fingers and in the toes; further than this sensation could not be tested. There was no definite paralysis anywhere, though the general weakness was extreme. Reflexes in the arms were moderately increased, the knee jerks were active, the Achilles tendon reflexes were very active. The plantar response was uncertain. There was a marked fluctuation in attention.

Necropsy.—The patient died Aug. 25, 1916. The following findings in the order of their importance, were abstracted from the necropsy report:

There is a very marked general anemia with marked pallor of the tissues of the body, of the brain, and of the spinal cord. A marked hyperplasia of the red bone marrow in the ribs and in the bodies of the vertebrae is noted. There are marked fatty changes present in the myocardium, producing the so-called "thrush breast" heart, in the pancreas, kidneys and liver. The spleen is absent, but a small accessory spleen is found. The proximal end of the splenic vein and the distal end of the splenic artery are occluded by scar tissue. Healed atrophic scars are present in the midline and in the left rectus region. Fibrous adhesions are found between the great omentum and the peritoneum, adjacent to the left rectus laparotomy wound, and between the transverse colon and the midline laparotomy scars. There is a moderate nodular fatty change in the lining of the aorta and in the aortic and mitral valvular leaflets. The distribution of the yellow material of the adrenal cortices is uneven. A slight hypostatic bronchopneumonia of the dependent portion of the right lung and a moderate bilateral hypostatic edema and hyperemia of both lungs are present, and slight

petechial hemorrhages are found in the visceral pleura of the dependent portions of both lungs. There is a marked hyperemia and a hyperplasia of the mesenteric, retroperitoneal, biliary, lateral lumbar, and iliac lymph nodes. A white stellate scar in the mesentery of the small bowel is noted. The costal cartilages show a partial ossification. The mastoid and petrous temporal bones are unusually cellular. There is an absence of two toes on the left foot and an atrophic scar is present over the right knee. The head is partly bald and the teeth are absent. A large persistent membranous Eustachian valve is seen. The prepuce is redundant and there is a slight phimosis. Sections from the liver for histologic examination show a slight congestion, marked fatty degeneration, and small areas of focal necrosis. The heart shows very marked fatty changes. The pancreas is normal. The adrenals show a moderate amount of fat. The lungs show a bronchial pneumonia. There is a chronic interstitial nephritis and the kidney tissues are infiltrated with leukocytes. Muscle tissue from the chest wall is negative. The weight of the spleen is 558 gm. and there is a slight chronic splenitis with cellular degeneration and a perisplenitis.

Weigert sections of the spinal cord are practically normal in appearance, with the exception of possibly a little thinning out of the fibers in the posterior columns in the upper thoracic portion. The Marchi sections of the spinal cord show a very extensive and comparatively recent combined sclerosis, such as is found in cases of pernicious anemia, the degeneration being most marked in the lower cervical and in the upper thoracic segments.

Brain.—The dura is normal in appearance, though very pale, and the sinuses are empty. The brain is almost a pearly white, the size and the contour of the gyri being normal in appearance. The leptomeninges show a moderate amount of edema and are very slightly clouded. The ventricles appear to be normal. The arteries at the base show a very slight degree of thickening but no atheromatous changes.

Weigert Sections: Frontal sections: Five or ten foci, of the type found in the spinal cord, are seen in the medullary substance of these sections, some of them being related to blood vessels while others were not, so far as could be determined. *Sections cutting through the brain just posterior to the chiasma:* With the unaided eye one can see a half dozen or more areas of pallor, ranging in size from 1.5 mm. to 3 or 4 mm. in diameter. The largest of these are seen in the white matter of the third frontal convolution on the right side; another, 3 mm. in diameter, is seen located near the middle of the corpus callosum and still two others of about the same size in the temporal lobe on the left. A distinctly pale area, somewhat triangular in shape, and about 2.5 mm. in diameter, is seen at the juncture of the inner and outer portions of the right globus pallidus, just above the anterior commissure. Under the microscope, these foci appear in large numbers and vary considerably in size and shape, most of them being independent of blood vessels. The area in the globus pallidus is seen to be caused by a destruction of the medullated fibers passing through that portion and a paling of the surrounding gray matter. *Sections through the crus:* Twenty or thirty such areas can be seen with the unaided eye, located in the white matter. These resemble the plaques described above, save that they are more numerous, though somewhat smaller. Marked ballooning of the fibers is noted. The plaques themselves present very irregular margins and are elongated in the direction of the fibers; some of them give evidence of having become enlarged by fusion of two or three separate areas. *Sections through the occipital lobes:* Some fifteen to twenty of these plaques can be seen grossly. These are distributed more or less uniformly throughout the white matter, though the fourchette contains relatively more of them. Sections through the middle of the pons are perfectly normal in appearance.

Marchi Sections: Sections through frontal lobes at the level of the genu of the corpus callosum: There is a diffuse degeneration of moderate intensity throughout the section, with a corresponding degree of perivascular accumulation. A few foci appear in which the degeneration is particularly marked. The

corpus callosum shows no more degeneration than is seen in other parts of the section. The cortical cells of the gray matter contain the normal amount of pigment. *Sections through the chiasma:* This section shows the same changes as the one just described, the fibers of the internal capsule sharing in the degeneration. *Sections passing through the brain 1.5 cm. posterior to chiasma:* There is a very extensive degeneration, rather general in its distribution, throughout the medullary portion of the section. This degeneration becomes somewhat more marked in the vicinity of the corpus callosum and of the pyramidal tracts, where the fibers appear swollen and sometimes resemble chains of beads. In the centrum semiovale, both right and left, a number of very small deposits of blackened granules are found, which presumably represent early stages of disintegration corresponding to the Lichtheim foci. There is also some perivascular deposit present. In general, the cells of the marginal gray, as well as those of the basal nuclei, appear to be normal. *Sections through the crus:* Grossly, one can see a number of lighter foci in the medullary substance, which probably correspond to some of the areas seen in the Weigert sections. There is a diffuse and very well marked degeneration present which seems to be almost as intense in the short association fibers going from one gyrus to another as it is in the longer commissural tracts, the degeneration being little more marked in the corpus callosum and the crus than elsewhere. While some of the cortical cells appear excessively pigmented, the average amount of pigment probably does not exceed the normal. *Occipital sections:* With the unaided eye the same pale areas appear in these sections as already noted, which microscopically, at times, show a pigment deposit at their peripheries. As in the preceding section, so here, we find a well marked and diffuse degeneration of the white fibers; this is particularly intense in the fibers of the splenium and of the optic radiations. Perivascular accumulations are commensurate with the degree of degeneration noted. In the cells of the gray layer, overlying some of the superior convolutions, one can note a considerable amount of pigment; the degeneration of the white fibers springing from this portion of the cortex is, however, not more marked than that occurring in the fibers located in the medullary rays of other convolutions. *Sections through the cerebellum:* There is a moderate degree of degeneration in practically all of the cerebellar laminae, with a corresponding deposit of detritus in the perivascular spaces. There appears to be no abnormal pigmentation in any of the Purkinje cells. *Sections through the pons at the level of the decussation of the fourth nerves:* There is a very definite and rather marked degeneration in the fibers of the median lemniscus, as well as a rather moderate amount of degeneration in the decussating fibers of the fourth nerve. A slight degree of degeneration is also observed in the reticular formation, in the fibers of the posterior longitudinal bundle, and in the pyramidal tracts; in these structures, however, the degeneration is very slight in degree and of questionable significance. Other structures appear to be practically normal. *Sections through the cord immediately below the pons:* There is a definite, though slight, degeneration present in the location occupied by the spinocerebellar tracts, particularly on one side. The remainder of the section, though showing a slight stippling, is probably negative. *Sections through the olives:* A fairly well marked degeneration is noted in the location occupied by the spinocerebellar tracts and a somewhat less marked but more recent change in the fibers of the median raphe. The fibers of the pyramidal tracts show a still less, though quite definite, degeneration.

Bielschowsky Sections: In the Bielschowsky sections a number of foci, about 0.3 mm. in diameter, are found which are oval, the long axis lying in the direction of the fibers. These show in their centers a marked thinning out of the axis cylinders, so that only a few of them are seen here, compared to the number seen in the surrounding tissue. In the thalamus a very similar area is noted. The cells appear to be normal and the neurofibril stain fairly satisfactory. As seen in the Ramón y Cajal gold sections, the glia fibers appear to be more massive, wavy, knotted and irregular in contour than is noted in any of the

control sections. The hematoxylin and eosin sections show a number of foci in the white matter which resemble localized patches of edema, in that the fibrillar structure is here somewhat crowded aside and the interfibrillar meshes enlarged. In one case, the center is formed by a more or less structureless and apparently necrotic mass. In all other respects the sections appear to be normal, and nowhere is an increase in glia cell nuclei apparent.

In sections stained with thionin and toluidin blue, particularly those chosen from the right and left Rolandic areas, and somewhat less so in those from the temporal areas, are seen numerous areas which resemble the foci described in the hematoxylin and eosin sections, save that the change is carried still further, the entire structure resembling a gland. The pyramidal cells, on the whole, are practically normal in appearance, save for a slight degree of vacuolization and some satellitosis. A number of the cells show changes which are somewhat more marked; thus, in one cell there is a perinuclear tigrolysis, the nucleus being stained a deep blue and the nuclear membrane very indistinct. This cell somewhat suggests the picture seen in axonal degenerations. The Nissl bodies, however, are, in general, well preserved. In the *Lichtgruenfuchsin* sections a few pyramidal cells are noted which contain a small number of fuchsinophilic granules; a number of others, however, are literally packed with large-sized, brilliant red granules. The blood vessels are normal in appearance and the vessel walls uniformly thin.

CASE 5.—(Necropsy 16-15.) *History*.—S. O. H., 51 years of age, Norwegian, single, was admitted to the hospital on the medical service Sept. 24, 1914. He was born in Wisconsin where he lived for three years, and then came to Minnesota where he lived most of the time. For twenty years he was a storekeeper in a small town, but the past year changed his occupation to that of selling postcards. His average weight was 200 pounds, which in the last four years decreased to 150 pounds. The father died at 60 of kidney trouble and the mother at 50, presumably of heart disease. The patient had four brothers, two of whom were living and well; the other two were said to have had fits and died in the attacks when young men. There were four sisters, one living and well and three dead from unknown causes. The patient generally slept well and his appetite had been good until recently. The bowels had been severely constipated most of the time. He did not use tobacco and denied using drugs. Up to three years previous to examination he used alcohol to excess, but the last few years took only an occasional glass of beer. Eight years prior he contracted gonorrhea, which became chronic, discharging for at least two years. As a boy he was always healthy, but when he grew up his stomach began bothering him off and on, the attacks of gastric distress coming on after drinking hard and lasting for about a week. He had about two of these attacks, on the average, in a year. He was otherwise well until the present trouble began. About two years previously he began having rheumatic pains in the feet which gradually worked up the legs into the body. He also had frequent attacks of gastric distress, which, however, were no longer associated with drinking. His feet became numb and in the previous summer he noticed that he would frequently stumble at night or, if he turned quickly, would fall. There was also a sensation of oppression around the abdomen which was accompanied by general pain and tenderness. Although these symptoms have been gradually growing worse, the patient was able to continue working until September 23, the night before he entered the hospital.

Physical Examination.—A physical examination showed the patient to be fairly well nourished, but very pale and somewhat yellowish in color, with a slight puffiness under the eyes. There was a marked pyorrhea, and most of the teeth were missing and replaced by plates. A slight eczema marginatum was present on the penis and scrotum. There was also some edema present in the legs. Aside from this, physical examination was practically negative. The blood pressure was 100 systolic and 72 diastolic. A urine analysis, made

September 25, showed nothing abnormal; November 25 it was found to contain a trace of albumin and some leukocytes. December 19 an analysis showed urobilinogen 3+ and urobilin 3+; there were no amino-acids present. Examinations of the stool December 18 and 28 revealed no ova or parasites. A Wassermann test of the blood was negative. The spinal fluid showed a Nonne-Appelt. Phase I negative, four small lymphocytes to the cubic millimeter and negative Wassermann. The results of the blood examinations were as follows: September 25, 80 per cent. hemoglobin, 5,000 leukocytes; October 7, 80 per cent. hemoglobin, 8,200 leukocytes, 4,900,000 red cells, marked anisocytosis, marked poikilocytosis, and slight polychromatophilia; October 20, 75 per cent. hemoglobin, 6,400 leukocytes, 4,700,000 red cells; November 7, 55 per cent. hemoglobin, 6,700 leukocytes, 2,000,000 red cells, and a color index of 1.37; November 19, 50 per cent. hemoglobin and a differential count of 74 per cent. polynuclear neutrophils, 23 per cent. small lymphocytes, 2 per cent. mononuclears, 1 per cent. eosinophils; November 30, 50 per cent. hemoglobin, 5,700 leukocytes, 1,900,000 red cells, and a differential count of 74 per cent. polynuclear neutrophils, 24 per cent. lymphocytes, and 1 per cent. eosinophils; December 7, 30 per cent. hemoglobin, 3,500 leukocytes, 1,500,000 red cells, poikilocytosis, anisocytosis, and megaloblasts; December 20, 35 per cent. hemoglobin, 3,000 leukocytes; January 2, 1915, 4,000 leukocytes, 1,400,000 red cells; February 5, 35 per cent. hemoglobin, 4,100 leukocytes, 752,000 red cells.

Neurologic Examination.—The neurologic examination disclosed the following: The nose was normal to inspection and the sense of smell, as tested with perfume, soap and other articles on his stand, normal. The patient could read bold faced type of about 5 mm., but could not read finer print of 2 mm. The field of vision was normal to a rough test. There was no strabismus, exophthalmos or diplopia. A slight horizontal nystagmus, which developed on looking toward the extreme right or left, coming on after a slight fatigue of the ocular muscles, was noted. The movements of the eyes were normal in all directions and convergence was good. The pupils were circular, equal in size and moderately contracted, with a normal reaction to light and accommodation, both direct and consensual. Sensation over the distribution of the fifth was normal for touch, pain, and pressure. The corneal and conjunctival reflexes were normal. Movements of the jaw, both horizontal and vertical, were normal in amplitude but somewhat deficient in power. The patient could wrinkle his forehead, close his eyes, and move his lips normally, save that in showing his teeth the left angle of the mouth was retracted a little further than the right. The ears were normal to inspection and hearing slightly impaired; the Weber, Rinne, and Schwabach tests were normal. There was no tinnitus and the patient rarely had vertigo, which might come on when the patient attempted to sit up. There was no difficulty in phonation, breathing or swallowing. The palate moved normally and the palate and pharyngeal reflexes were present. Pulse was normal in rate. The sterno-mastoid and trapezius muscles were normal, save for a slight deficiency in power. The tongue was protruded in the midline, showed no atrophy or fibrillation, but presented a slight general tremor, with slight impairment in power. There was subjective prickling of the fingers and of the toes. Sensation, as tested with cotton, appeared to be diminished on the palmar surface of the right hand below the level of the wrist and on the dorsum, below the middle of the second phalanges, of all fingers, and on the distal phalanx of the thumb. On the left hand, cotton touch was about normal. In the feet the sensibility to cotton touch was impaired on both sides below a point 4 inches above the external malleolus and 2 inches above the internal malleolus. Pain sensibility was normal in both hands and feet; and both touch and pain sensibility were normal over the rest of the body. Vibration sensation seemed to be impaired below the right wrist and was altogether absent over the head of the fifth metacarpal bone and digit. It was slightly diminished on the left hand below the wrist, but was nowhere entirely absent. There was complete paresthesia below the middle thoracic vertebra. Muscle pain sense and sensitiveness of

the nerve trunks were normal. The finger to finger and the finger to nose tests were fairly well performed, but there was a definite ataxia in both legs which became evident in the heel-knee-toe test. The patient was at times unaware of the exact location of his legs in the bed. Joint sense in the toes was completely absent, though the patient knew which toe had been touched. There was a very marked Romberg. There was general muscular weakness, and the patient was unable to stand without assistance. Nowhere is there localized atrophy or fibrillation. The extensor power of the legs was less than the flexor power. There was no tremor present in hands or legs. The conjunctival, corneal, palate, and pharyngeal reflexes were normal. The biceps, triceps, and supinator reflexes were normal and equal on both sides. The abdominal, cremasteric, and external anal reflexes could not be elicited. The plantar reflexes were extensor on both sides by Babinski's method, and on the left side by Oppenheim's method. The patellar and Achilles tendon reflexes were absent, even on reinforcement. There was no ankle or patellar clonus. The patient complained of inability to control the movements of the bowels and at times of difficulty in holding the urine. Sexual power was absent. There was a slight edema of the subcutaneous tissues.

Mental Examination.—(1) General memory and orientation: Memory for past and recent events appeared to be fairly good and the patient related childhood experiences with apparent accuracy. The patient said that he entered the hospital September 23, since when he thought he had greatly improved. He gave the month as December, which was correct, and the year as 18—then says 1900. Was oriented as to place and persons. (2) General understanding and insight appeared to be satisfactory. (3) Emotional status: He was depressed, as a rule, and had been so for years; however, he had no suicidal tendencies, but said, on the contrary, that he expected to be hopeful to the last minute. He complained of having had a good deal of trouble with the devil, who, twenty-five years ago, while the patient was in perfect health, got into the habit of appearing after he had gone to bed at night. At these times he would bend over the patient and hold him so firmly at his sides that he would awake from the pain. A good deal of prayer finally rid him of this trouble, until the past September when the devil again appeared, tormenting him almost every night for about a month. One night, while sleeping in a boarding house, the devil entered and carried on to such an extent that the screaming of both him and the patient caused the neighbors to send in a call for the police. He added that, though he was usually asleep when the devil appeared, he was well awake for some time before he left. The patient is convinced that God sent these visitations as a punishment for his past iniquity. At times he heard the church bells ringing, usually in the left ear, for half an hour at a time. Also heard whistling, and words which come from various directions but say nothing. (4) Memory: Memory for past and recent events appear to be fairly good, though the patient said that of late it had grown poor. In repeating the "Cowboy Story," he got to the point at which the cowboy put on his old clothes, but forgot all that followed, omitting the dog from the story altogether and remembering absolutely nothing about it. He was able to repeat numbers of four places correctly, but made mistakes in repeating numbers of five or more digits. In repeating the alphabet he gave the last letters as q, u, s, t, y, z. (5) Attention: Attention during the entire examination was found to be satisfactory, the attention tests being performed fairly well. (6) Thinking: He could do simple calculations, but could not point out the faulty logic in the "Lillies and Roses" test. (7) Capability: Save for the limitations imposed by his weakness the patient's capability appears to be good. There is some slurring in repeating the test phrases. (8) Association: In the Masselon tests, the patient was unable to build sentences that were to contain three given words. Being asked to make a sentence containing the words "kettle," "water" and "stove," he said, "The kettle stood in the water," and in using the words "baby," "bottle" and "milk," he said, "The baby was drinking the bottle." (9) Sleep and dreams: The patient sleeps

poorly as he is awakened by the least noise. The jerking in his legs also tends to keep him awake.

Necropsy.—The patient died March 18, 1915, necropsy being performed thirteen hours postmortem. The protocol showed the following: *External appearances:* The body is that of a well developed, fairly well nourished, adult male, 179 cm. in length. Rigor is present, and there is lividity in the dependent parts. The pupils measure 5 mm. in diameter and are equal. There is a moderate amount of edema in the extremities and in the external genitals. There is a small pigmented mole at the angle of the left scapula. *Peritoneal cavity:* The peritoneal cavity contains about 2,000 c.c. of clear, straw colored fluid. The serous surfaces are smooth and clear and there are no adhesions. The appendix measures 9 cm. in length and hangs free. The diaphragm reaches the fourth interspace on the left and the fourth rib on the right. The mesenteric lymph nodes are moderately enlarged and dark in color. *Pleural cavities:* The left pleural cavity contains 800 c.c. and the right, 500 c.c. of a clear, straw colored fluid. There are strong fibrous adhesions at the apex and at the posterior portion of the base of the right lung. The left pleural cavity is free from adhesions and the serous surfaces are smooth and clear. *Pericardial cavity:* The pericardial cavity contains about 250 c.c. of clear, straw colored fluid, the visceral and parietal pericardium being smooth and glistening. *Heart:* The musculature is thin, soft, flabby, and somewhat pale in color. The mural endocardium is smooth and clear and the valve leaflets show no gross lesions. The root of the aorta has a few elevated, yellowish patches, but possesses good elasticity; the intima is of a bright red color. *Lungs:* No nodules are palpable and the lungs crepitate throughout. From sections through the posterior portion of the base of the left lung, a large quantity of thin, reddish fluid can be expressed. *Spleen:* The spleen weighs 200 gm., the capsule is smooth, and the pulp is dark in color and scrapes readily. *Liver:* The liver weighs 2,850 gm., is of a fairly light, reddish brown color, and on cut section reveals small, dark areas surrounded by lighter zones. The pancreas, gastro-intestinal tract, and adrenals show no gross lesions. *Kidneys:* The kidneys together weigh 360 gm., are equal in size, and slightly lighter in color than normal. The capsules strip readily, leaving smooth, glistening surfaces. The cortices are of even thickness and the normal markings regular. The bladder is normal. The bone marrow from the upper third of the femur is yellow in color. The anatomic diagnosis was (1) pernicious anemia (aplastic type); (2) ascites, hydrothorax, and hydro-pericardium; (3) moderate chronic passive congestion of the liver; (4) hypoplasia of the mesenteric lymph nodes; (5) slight atherosclerosis; (6) edema of the left lung; (7) hemoglobin imbibition of the aorta.

Sections of the spinal cord stained by the Weigert method show a moderate degree of combined sclerosis of the type seen in pernicious anemia. The Marchi sections of the cord are normal in appearance.

Brain.—The brain is slightly paler than normal. The leptomeninges are slightly clouded along the blood vessels of the convexity. The vessels at the base are possibly a little thickened. The gyri are normal in size and conformation. The ventricles are normal in size and the ventricular walls smooth and glistening.

Weigert Sections: Sections passing through the brain at the level of the *genu corporis callosi:* In the marginal gray matter one sees areas of increased pallor at the dividing point of the blood vessels. The medullary portion of the section is absolutely normal in appearance. Sections through the optic chiasma, 1 cm. posterior to the optic chiasma, and the crus, are normal. Occipital sections show a slight degeneration of the medullated fibers in the neighborhood of some of the blood vessels. In the marginal gray small circular foci, as described in a number of preceding cases, are found in limited numbers. Sections through the pons are normal. Sections through the olive and the cerebellum: Just underneath the dentate nucleus of one side appear two small foci of the Lichtheim

type. In one of the recesses formed by the folding of the dentate nucleus, the white fibers show definite ballooning and disintegration.

Marchi Sections: In the right centrum semiovale are seen evidences of recent degeneration, a number of the fibers appearing swollen and in many places represented by rows of blackened globules. These changes become progressively more marked in the deeper portions of the brain. All of the degeneration seen appears to be recent, none of the blood vessels showing evidences of perivascular accumulations.

Bielschowsky Sections: In the Bielschowsky sections a number of blood vessels can be seen which are surrounded by a light halo, the fibers within this area showing evidences of disintegration. The Weigert glia fiber and the Ramón y Cajal glia cell sections show no evidence of reaction on the part of this tissue. Here and there, in the meninges and in certain of the blood vessels there is seen rather extensive invasion of streptococci, but no evidence of reaction. In the hematoxylin and eosin sections rather numerous sieve like areas are noted in the medullary substance of the cortex, which vary in size from 0.01 to 0.03 mm., and which, in a number of instances, are found to be definitely related to the blood vessels, though this relation cannot be definitely established in all of them. As many as eighteen to twenty of these foci can be counted in the low power field of the microscope. One of the meningeal vessels was found to contain a good many leukocytes. Thionin, toluidin blue, and neutral red sections show most of the pyramidal cells to be absolutely normal in appearance. In a few instances, however, there are found chromatolysis, slight satellitosis, neuronophagia, indistinctness of the cell outline with disappearance of the processes, and some swelling and eccentricity of the nuclei. In a good many cells there appears, plastered around the nucleus and the periphery of the cell, a rather deeply staining material which is evidently derived from the Nissl bodies. A very few of the cells exhibit a certain degree of vacuolization. The changes noted above are found to be most numerous in the Rolandic area. The blood vessels at the base show some thickening of the intima and possibly also some of the media; there is a moderate increase in the elastic fibers and some splitting of the inner elastic membrane. The *Lichtgruenfuchsin* sections show nothing pathologic.

CASE 6.—(Necropsy 251.) History.—A. T., 37 years of age, Norwegian, died on April 15, 1913, a clinical diagnosis of pernicious anemia having been made by a competent internist. Necropsy was performed twenty-three hours post-mortem, a standard embalming fluid having been injected the evening before. The following notes appear on the record:

Necropsy.—The body is that of a somewhat emaciated, but well developed adult man. There is moderate rigor mortis and slight lividity of the dependent portions. Mucous membranes of the throat and mouth are very pale. The plural cavities contain about 10 ounces, on the right side, of a clear, yellowish fluid which contains some flakes of fibrin. The pericardial cavity is empty and the walls smooth and glistening. The abdominal cavity contains no fluid and the viscera, save for pallor, are normal in appearance. **Lungs:** The right lung weighs 760 gm. The lower lobe is heavy and does not collapse. The upper lobe, in its dorsal portion, is firm and crepitates feebly, the anterior portion being very pale and normal to the touch. On cutting the lower lobe a pale, yellowish red-fluid escapes and a number of granular plugs may be scraped out. The posterior portion of the upper lobe was filled with a frothy fluid. The left lung weighs 650 gm. and is very pale and edematous. The peribronchial lymph nodes are pigmented and slightly enlarged. **Heart:** The heart muscle is pale and flabby in consistency. The right cavity is filled with a thin, pale bloody fluid. The left cavity contains a white coagulum; the walls are fixed to a certain depth by the embalming fluid. The valves are normal in appearance. The aorta is negative. **Spleen:** The spleen weighs 300 gm., is somewhat enlarged, pale and firm. **Kidneys:** The combined weight is 390 gm., the right being a little smaller

than the left. The surfaces show the fetal markings. The capsule is slightly thickened and strips with a little difficulty, small bits of the cortex being removed with it. The cortex is somewhat narrow, the normal markings somewhat indistinct, and the glomeruli rather prominent. The left contains a solitary cyst about 1 cm. in diameter. The ureters, bladder and urethra are negative. *Adrenals:* These are normal in size, but very pale. *Liver:* The liver weighs 1.630 gm. The capsule is smooth, rather pale and has a rusty tint. The gall-bladder is filled with a viscid bile and the ducts are patent. The pancreas is negative, though very pale. *Stomach:* The stomach is dilated with a liquid content; the wall is very pale, somewhat thinner than normal, and the mucosa shows no evidence of old ulcers or other irritation. The small intestine is pale and contains small amounts of fluid feces, but is otherwise negative. The appendix hangs free and is normal in appearance. The large intestine contains considerable amounts of feces in masses. In places the wall of the intestine is very thin. *Retroperitoneal structures:* The glands about the aorta and the celiac axis are enlarged and somewhat congested. The scalp and the skull are negative. *Bones:* The clavicle contains marrow which is normal in appearance. The ribs and sternum contain a very friable and pultaceous marrow which is a deep reddish chocolate color. Smears from the sternum and from the marrow of the fifth rib stained with the Erlich-Biondi stain show erythrocytes, microcytes, polychromatophilia, many megaloblasts, some normoblasts, and white blood cells of all types, including many myelocytes and coarsely granular oxyphils. Necropsy diagnosis: (1) Anemia of all the viscera; (2) lobar pneumonia of the right lower lobe, with a serofibrinous pleuritis; (3) edema of the left lung and the upper lobe of the right lung; (4) some fatty degeneration of the kidney; (5) slight dilatation of the heart, with possibly some fatty degeneration of the muscle; (6) increase in the red bone marrow; (7) atrophy and dilatation of the stomach; (8) extensive pigment deposit throughout the liver. Unfortunately none of the spinal cord was removed at necropsy.

Brain.—The membranes of the brain are very pale. The brain itself is normal in appearance and consistency, save that it is almost pearly white in color. The blood vessels at the base of the brain are normal in appearance and very delicate to the touch.

Weigert Sections: These are all normal save for a few slight changes. *Frontal area:* In the marginal gray matter and in the medullary substance at various distances from the surface are a number of light circular areas, about 0.1 mm. in diameter, which are often seen surrounding capillary vessels cut in cross section. *Section through the optic chiasma:* Surrounding a number of the smaller capillaries in the medullary substance of the brain there is a small area of disintegration, such as have been described. *Sections through the crus:* A few circular pale areas, present up to the number of about five to the low power field, and measuring about 0.25 mm. in diameter, are seen in some of the medullary rays of the gyri. Similar areas are also seen in the marginal gray layer. *Occipital lobes:* Sections from this area resemble in all respects those just described. Sections through the cerebellum are normal in appearance.

The Marchi sections show no definite pathologic changes. In both the gray and the medullary portions of the cortex, as seen in the Bielschowsky sections, there are noted pale, more or less circular areas, about 0.1 to 0.25 mm. in diameter, present in numbers up to four or six to the low power field (No. 3 Leitz objective and No. 4 eye piece) and resembling in all respects similar areas described in some of the foregoing cases. Serial sections show that these, in nearly every instance, are related either to some small blood vessel or surround one of the pyramidal cells of the gray layer. The cells themselves, lying within these areas, show no pathologic changes. The glia structures in this brain are normal in appearance, with the possible exception of some irregular thickening of the coarser glia fibers. Hematoxylin and eosin sections show the same areas of disintegration described in the Bielschowsky sections, the association with the perivascular spaces being well illustrated. The cells of the cortex, as stained

with thionin and toluidin blue, are absolutely normal in appearance, with the exception of a small number of cells lying within the degenerated areas, described in the preceding sections. These are more readily studied in sections which are somewhat overstained. No fuchsinophilic granules are noted. The larger blood vessels at the base are normal in appearance.

CASE 7.—(Necropsy 11-17.) *History.*—H. R., 42 years of age, single and a laborer, was admitted to the hospital Jan. 25, 1911, complaining of difficulty in breathing, fatigue on slight exertion, a pain about the heart which was sharp at times, some swelling of the face, and increasing pallor of five weeks' duration. The patient was born in Minnesota and had never left the state. The father and mother both died of unknown causes. His habits were said to have been moderate.

Physical Examination.—This showed a middle aged man, medium in stature, well developed, and fairly well nourished. The hair was brown, with an admixture of gray. The eyes were blue, the pupils circular, equal in size, and normal in reaction. Hearing was normal. The patient stated that he had had some ringing in the ears prior to coming to the hospital, but this had now wholly disappeared. The skin was somewhat yellowish in color and extremely pale. The mucous membranes were pale and the capillary circulation did not return promptly after pressure. The left border of the heart extended to about 1 inch outside of the nipple line. There was a blowing sound, systolic in time, heard loudest over the apex, and transmitted over the entire chest. The abdomen was negative to palpation, and no masses were felt. The muscles were somewhat flabby and there was a moderate loss of strength. The spleen was large and palpable. The deep reflexes were diminished in the upper extremities and the knee kicks could not be obtained. There were no enlarged glands palpable. The urine was normal save for an occasional pus cell. Examination of the stool showed no ova or parasites. Examination of the blood showed the following: January 28, hemoglobin 18 per cent., red count 800,000 and 2,500 leukocytes; February 9, hemoglobin 10 per cent., red cells 400,000, 7,000 leukocytes, with an apparent increase in the relative number of lymphocytes, a rather marked poikilocytosis, polychromatophilia, also normoblasts in moderate numbers and megaloblasts in greater numbers. The patient exhibited a slight rise in temperature, which fluctuated, but never exceeded 99.6 F. The pulse varied between 80 and 100, and the respirations between 20 and 24. The patient was put on dilute hydrochloric acid and nux vomica. February 6, there was slight epistaxis. He became progressively weaker and on February 10 became very delirious, talking and moving about continually. He died February 11.

Necropsy.—Necropsy was performed five and a half hours after death with the following results: *External appearance:* The body is that of a fairly well developed, poorly nourished, adult male, 168 cm. in length. The skin is very pale and mottled on the arms and neck by freckle patches. Rigor mortis and lividity are absent. The pupils measure 6 mm. and are equal. There is no edema, cyanosis or jaundice. *Peritoneal cavity:* The surfaces are everywhere pale but smooth and glistening. The right lobe of the liver in the midclavicular line reaches 3 cm. below the costal margin. The left lobe of the liver is very prominent, reaching 11 cm. below the xyphoid cartilage. The appendix is 7 cm. in length and is bound by adhesions to the root of the mesentery, on the left side at its tip. Near the tip the lumen of the appendix is obliterated. The mesenteric lymph nodes are normal. The diaphragm reaches to the fifth space on the left, and to the fifth rib on the right. *The pleural cavity:* The pleural cavities are interrupted by numerous stretched fibrous bands. There is no free fluid in the cavity. The pericardial cavity is normal, except for a large grayish white patch on the anterior surface of the right ventricle. *Heart:* The heart weighs 418 gm. The muscle is very pale but of firm consistence. The cavities are filled with clots and are all somewhat dilated. These clots are composed of definite layers, the upper portions having the appearance of "goosefat," while

the lower layers are much paler than normal. The valve leaflets are apparently normal. The root of the aorta shows an occasional raised grayish patch of thickening. The tricuspid valve measures 15 mm., the pulmonary valve 8 mm., the mitral valve, 9.5 mm., the aortic valve 8 mm. The depth of the right ventricle is 10 cm., and the thickness 0.6 cm. The depth of the left ventricle is 9.5 cm. and the thickness, 1.4 cm. *Lungs:* The lungs are quite pale and remarkably free from black pigment. There is no evidence of postmortem congestion of the dependent portions. The lung pulp is free from nodules or tubercles. In the peribronchial lymph nodes of the left lung there is one small calcareous nodule. A similar nodule exists in the lymph node at the bifurcation of the trachea. *Spleen:* The spleen is small and regular, weighing 85 gm. The pulp is increased in consistence, of normal color, and on cut surface, aside from comparative obscurity of the malpighian bodies, appears normal. *Liver:* The liver weighs 1,695 gm. The surface and pulp are pale and very moist, the pulp having a swollen feeling. The gallbladder is distended with thin bile and the ducts are normal. *Gastro-intestinal tract:* The mucous membrane throughout is very pale. The pylorus shows apparent definite thickening, but there is no evidence of any lesion throughout the tract. Peyer's patches, in the lower portion of the ileum, are raised, prominent, and slightly roughened on their surfaces. *Adrenals:* The adrenals are free from demonstrable lesion. *Kidneys:* The kidneys weigh 310 gm. The capsules strip readily, leaving smooth surfaces. The pulp of the left kidney is very pale and the markings are indistinct. In the pulp of the right kidney, there is a slight yellowish tinge in the cortical portion, and the striae are fairly regular. The bladder is distended with a clear urine. *Genital organs:* The prostate shows occasional dark pigmented points. The aorta contains numerous raised, grayish white or grayish yellow nodules. *Organs of the neck:* The thyroid and trachea are normal. *Head:* The scalp, calvarium, and dura are normal. The base of the skull and the middle ears are normal in appearance. *Bone marrow:* The bone marrow of the right femur throughout its entire extent is very red, soft, and of a thick, oily consistence. The bone marrow of the ribs is very red and prominent. The necropsy diagnosis is: (1) primary anemia of an acute type; (2) old healed tuberculous pleuritis; (3) edema of the brain; (4) chronic obliterating appendicitis; (5) possible thickening of the pyloric ring. *Bacterial examination:* A culture from the heart's blood is negative. *Microscopical examination:* The muscle fibers of the heart are in good condition. There is almost complete absence of blood from the capillaries. There is a patch of scar tissue under the pleura and some emphysema. The spleen is normal. The liver shows no blood in the sinuses. The hepatic cells show an increase of pigment and large numbers of fat droplets. The stomach is normal except for a little postmortem change, which is also true of the intestinal tract. The adrenals are normal. The convoluted tubules of the kidney are somewhat dilated, the epithelial cells are in good condition, and there is no increase in connective tissue. The aorta shows a slight thickening of the intima. The thyroid gland is normal. The sinuses of the lymph nodes are very prominent and contain large numbers of leukocytes, many of the polymorphonuclear type. The prostate is normal. The testicles contain no spermatazoa, but are otherwise normal. The pituitary gland is apparently normal. The bone marrow shows the typical structure of red bone marrow; there are large numbers of myelocytes, nucleated reds, etc., but very little adipose tissue cells.

Brain.—The brain weighs 1,305 gm. There is no distinct evidence of lesion except for a marked edema of the pia arachnoid and some pallor. The blood vessels are empty and slightly thickened at the base. The ventricles and gyri are normal. The spinal cord, of which sections could be obtained only from the extreme upper end, appears to be normal.

Weigert Sections: *Frontal area:* In the medullary portions of the frontal area are seen three blood vessels, surrounding which there is an evident destruction of the medullated fibers. *Sections through the optic chiasma:* Two

plaques about 0.2 by 0.4 mm. in size are seen, one in the corpus callosum, and the other in the white matter just under the marginal gray. These resembled in all respects the Lichtheim foci of the cord. *Sections through the crus and through the occipital lobes:* Aside from two or three small areas of destruction, these sections appear to be normal. *Sections through the cerebellum and through the pons* are normal. The Marchi sections of the cortex show a very slight stippling, which is probably pseudo-Marchi in character. A few ballooned myelin sheaths are found. There are no accumulations about the blood vessels.

Bielschowsky Sections: In the Bielschowsky sections a very limited number of lighter plaques, similar to those described in preceding cases were seen, both in the white and in the marginal gray. In this case, however, the association of these plaques with blood vessels or pyramidal cells was less constant. In all of the sections stained by the Ramón y Cajal stain and by the Weigert glia fiber method there appears to be some increase in the size of the glia cells, as well as some enlargement, and possibly some proliferation of the glia fibers. The hematoxylin and eosin sections show nothing abnormal save a marked satellitosis. Sections stained with thionin, toluidin blue, and neutral red show a well marked satellitosis, occasional tigrolysis, and eccentricity of the nuclei. In sections which are somewhat overstained one can see a number of the pale areas, both in the marginal gray and in the medullary portions, which are most numerous in the temporal lobes, where one or two can be seen in from one to six low power fields. Some of the pyramidal cells within these areas appear somewhat shrunken and rather deeply stained; others show a marked tigrolysis and vacuolization, with indistinctness of the cell membrane. The basal nuclei appear normal. No fuchsinophilic granules are seen in any of the sections. The larger blood vessels from the base show a slight, diffuse arteriosclerosis, which involves principally the media; also a slight and diffuse increase in the amount of elastic tissue.

DISCUSSION

Certainly it cannot be said that the cortex of pernicious anemia patients is barren of pathologic findings. The lesion of prime interest is, of course, the occurrence of plaques in the medullary substance of the cortex, which in every respect resemble the lesions so often found in the spinal cord. While the cases reported by Barrett all had a very marked mental disturbance associated with the pernicious anemia, this obtains in only one case of this series, the mental condition of the patient in the remainder being no more altered than is usually seen in pernicious anemia. In three of the seven brains studied, this focal degeneration could readily be seen with the naked eye, in two it was of moderate intensity, requiring a microscope for its detection, and in two it was very slight indeed, only a very few small areas having been noted.

The incongruity between cases presenting cord symptoms clinically and those showing pathologic changes at subsequent examination has long been a matter of comment; thus, also, in Case 4 there was marked clinical evidence of cord involvement, while pathologically there appeared only a very slight degeneration as shown in the Weigert sections, though in the Marchi sections this change was more evident. On the other hand, in the same case the mental symptoms were very slight and no change in the mentality appeared until just preceding death,

while the degenerative changes in the brain were very marked. If one considers only those cases in which there existed a definite psychosis, this lack of correlation between the clinical and pathologic findings is even more striking. Although Barrett found definite pathologic changes in ten of the eleven cases which he reports, the Lichtheim plaques were present in only four, and very insignificant in the mental case here reported; on the other hand, in four of the seven cases of this series, the degeneration was very marked, while the mental symptoms were no more marked than is ordinarily observed in pernicious anemia. Just what part these lesions play in the production of this mental condition cannot be definitely stated. As Barrett and others have shown, the development of well marked psychotic manifestations is probably independent of the pernicious anemia itself. The same lack of causal relationship between the mental symptomatology and the pathologic changes observed, probably obtains with reference to these plaques also. It is not at all unlikely, however, that they may aid in the production of the indifference, irritability, apathy, and somnolence so frequently seen, though the principal factor underlying these phenomena is probably the toxin itself.

The percentage of pernicious anemia cases showing pathologic lesions in the cord is rather high, though an accurate figure cannot be given. Nonne, in a series of seventeen cases, found cord changes present in ten, about 59 per cent. Minnich, in thirty cases, found changes in twenty-three, about 77 per cent.; Petré, in nine cases, found changes in two, about 22 per cent. In the five cases of this series in which the spinal cord could be studied, combined sclerosis was marked in three, moderate in one, and very slight in one.

Compared to this it will be seen that the degenerative changes in the medullary portion of the cortex occur fully as often in pernicious anemia, if not oftener, than do changes in the spinal cord, though the lesions in the brain are usually smaller, fewer in number, more widely scattered and not so readily enlarged by confluence and secondary degeneration, which renders their detection more difficult. In Cases 1, 2, and 3 there was a well marked change in both the brain and the spinal cord; in Case 4 the changes in the brain were marked while those in the spinal cord were relatively slight; in Case 5 the degeneration of the brain was very slight while that in the cord was moderate. If the results of such a small series of cases can be used in formulating a general principle, it might be said that the changes in the cord and in the brain run fairly parallel.

Of not less importance, however, are the smaller areas which were described in the Weigert sections as being more or less circular in outline, about 0.1 mm. in diameter, and most numerous in the medullary

portion of the cortex, just underlying the marginal gray of the convolutions. The same areas appeared in other slides as localized patches in which the fibrillar structure was more or less pushed aside, the meshes being thereby enlarged; the margins were not well defined, but graded almost insensibly into the surrounding tissue, the entire structure presenting a picture such as might be brought about by a localized edema. As serial sections showed, they may be unrelated to any blood vessels, though as a rule they tend to surround these like a halo. Axis cylinders passing through these areas were found to be more or less disintegrated, and in the center of a number of them was seen an accumulation of granular debris, as shown in Figure 13. There was no evidence of any associated glia reaction or cellular increase. In a number of instances these meshes were found to be more or less distended with a somewhat hyaline, usually basophilic substance, which resembled in every respect material found in the perivascular spaces, and with which it at times seemed to be continuous, as though it had been pressed into the tissues. Such a condition is represented in Figures 14 and 15. There appears to be but one conclusion, and this is the obvious one, which is that at least some of the white fibers, including the myeline sheaths and the axis cylinders, are destroyed, presumably through toxic action, possibly assisted by stasis, by a substance which accumulates in the so-called perivascular space. The very marked degeneration seen around some of the vessels in the Marchi sections, as well as the Weigert sections, supports this theory as additional evidence. It was also noted, however, that these perivascular structures were not the only ones in which this degeneration was initiated, but that a very diffuse and widely scattered destruction of the medullary substance at times occurred. To state that this is due directly to toxin action is rather arbitrary, though it certainly appears by virtue of its apparent simplicity to be the case, and it is not only possible, but also probable, that such a mechanism may obtain.

There is another factor, however, which the study of this material shows to be instrumental also in bringing about degeneration in the medullary substance of the cortex. It will be recalled that in Cases 2, 3, 6, and 7 certain areas of pallor, resembling very closely those just referred to, were also present in the marginal gray matter of the gyri. These were, in perhaps the majority of instances, found surrounding a pyramidal cell, as shown in Figures 16, 17, 18 and 19, the cell thus located presenting all degrees of degeneration from one which was practically normal in appearance to one which was completely disintegrated, the cells in the vicinity being practically normal as revealed by microscope. It seems indisputable that this cellular disintegration and the surrounding area of partial necrosis bear some relation to one

another. The interpretation of this, however, is not so simple. We are probably justified in assuming that the process at work here does not differ materially from that acting to bring about degeneration in other structures of pernicious anemia brains. Accordingly, this cellular destruction is probably the result of some toxin action, assisted possibly by some nutritive factors of mechanical origin. The manner in which this toxin is conveyed to the cell is probably the same as elsewhere, namely, through the lymphatic channels; incidentally this would serve as additional evidence of the existence of a so-called pericellular space of Obersteiner. Granting that pyramidal cells of the cortex may be thus destroyed, there would then follow a secondary degeneration of the axon to which it gives rise, which would account for at least some of the degenerating fibers seen in the cortical white matter.

Certain other cell changes were observed also, though, on the whole, the cells were practically normal in appearance. Among the changes seen, were varying degrees of tigrolysis, particularly in the cells of the second and third pyramidal layers, vacuolization, loss of cell processes, indistinctness of the cell outline, eccentric positions of the nuclei and of the nucleoli, some of which were very much swollen, deep staining of the nucleus, partial extrusion of the nucleus, and in two cases, definite axonal reaction. Satellitosis and neuronophagia were observed also. Fuchsinophilic granules were seen in the cells of a number of cases. In certain cells there appeared to be an increase in the amount of intracellular pigment which exceeded the normal; on the whole, however, this was not the case.

Relative to the glia changes, little can be said. There appeared to be in some of the cases a little increase in the coarser glia fibers, which often seemed enlarged, nodular, and very wavy. Henneberg's observation, that there is in general little glia reaction in cases of this kind, due possibly to the poor nutritional state, would seem to be borne out by these findings. Too much can hardly be said in praise of Ramón y Cajal's comparatively new gold stain for glia cells and the coarser glia fibers. We found it to yield very excellent pictures.

Hemorrhages were noted in but one case, and here they were not very numerous. Definite softening was observed in two of the cases, once involving a portion of the basal nuclei, and in another, the cortical white matter. The "Ringwallherdchen" described by Schroeder as being so characteristic of pernicious anemia brains, though carefully sought, could not be found, though it seems that this should be no difficult task, in view of his description. Only one focus, in which the resemblance was, as a matter of fact, exceedingly remote, was found which could possibly be interpreted as an accumulation of disintegrated glia cell nuclei.

SUMMARY

Summarizing again what we believe to be the most salient features in the pathologic anatomy of pernicious anemia brains, we have the following:

1. Not only do degenerated areas of the Lichtheim type, such as are typically found in the posterior and lateral funiculi of the spinal cord in pernicious anemia patients, occur in the medullary portions of the brains of these cases, but they occur with about the same frequency, though their demonstration may be rendered more difficult.
2. Patients who show degenerative changes in the spinal cord at necropsy, usually show the same type of lesion in the brain also.
3. In addition to these focal degenerative areas found in the white matter, which may or may not be associated with blood vessels, we also find a diffuse degeneration, which, though it is, as a rule, somewhat more striking in the long association tracts, also occurs in the short commissural fibers passing from one gyrus to another, thus rendering the view untenable that it is the distance of these fibers from their trophic centers which is instrumental in causing the degeneration.
4. The gray matter is by no means immune from the destructive process. This is usually focal in character, and begins around the pyramidal cells of the marginal gray layer, the cells themselves being ultimately destroyed in the process, this, in turn, giving rise to a secondary and very diffuse degeneration of the medullated fibers in the white matter.
5. Though some degeneration was noted in the fibers of the internal capsule and in the long tracts passing through the pons, the degeneration at this level was less intense than that seen either in the cord or in the brain.
6. The appearance of these plaques, not only around the blood vessels but also around some of the larger pyramidal cells, seems additional evidence that lymph stasis is an important factor in the production of these foci.
7. Well marked psychoses, such as are occasionally associated with pernicious anemia, probably have little or nothing to do with these destroyed areas.
8. The milder mental manifestations such as somnolence, apathy, and terminal delirium, are probably in a measure dependent on these lesions, though the chief causative agent of these symptoms is probably the toxin itself.

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